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WANGENSTEEN ANNIVERSARY ISSUE

Vol. 39 JANUARY, 1956 No. 1

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Wangensteen Anniversary Issue

Owen H. Wangensteen ---------- 1

Cardiojejunopexy for Coronary Artery Disease. Ivan D. Baronofsky, M.D., Donald W. Hannon, M.D., and Charles E. Turback, M.D., Minneapolis, Minn. ---------- 3

A Parenchymatous Surgical Approach to the Problem of Portal Hypertension. Davitt A. Felder, M.D., John J. Haglin, M.D. (By Invitation), and Thomas O. Murphy, M.D. (By Invitation), St. Paul, Minn. ---------- 7

A Study of the Genesis of Shock Associated With Experimentally Induced Hepatic Necrosis in Dogs. David State, M.D., and Irving Lichtenstein, M.D. (By Invitation), Los Angeles, Calif. ---------- 12

The Myenteric Plexus of the Pylorus: Its Early Normal Development and Its Changes in Hypertrophic Pyloric Stenosis. Stanley R. Friesen, M.D., James O. Boley, M.D., and Don R. Miller, M.D., Kansas City, Kan. ---------- 21

Endocrine Control of Mammary Glands in C_3H Mice. Donald J. Ferguson, M.D., Minneapolis, Minn. ---------- 30

The Production and Evaluation of Ascites Secondary to Isolated Tricuspid Insufficiency in Dogs. Mitchell W. Spellman, M.D., Ph.D., and Basdeo Balkissoon, M.D., Washington, D. C. ---------- 37

(Contents continued on inside back cover)

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SURGERY

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SURGERY

VOL. 39 JANUARY, 1956 No. 1

Wangensteen Anniversary Issue

OWEN H. WANGENSTEEN

In September of 1955, the former students of Dr. Owen H. Wangensteen joined with more than 700 of his friends and surgical colleagues to observe the twenty-fifth anniversary of his appointment as Professor and Chairman of the Department of Surgery at the University of Minnesota. This was a unique anniversary, for few men so young both in age and spirit have held such a position for a quarter of a century. To recount the accomplishments of these years would be an enormous undertaking; to assess their importance is hardly our role, for the patients and doctors throughout the world who have felt the impact of his research and teaching are eloquent witnesses to the magnitude of his influence. The occasion could not go by, however, without our giving recognition to his extraordinary qualities of inspiration and leadership as they have affected the lives of the many surgeons who have worked and studied under his guidance.

The plan for such recognition was conceived in the spring of 1953, when a group of former surgical residents founded the "Owen H. Wangensteen Surgical Education Foundation," constituted to "further objectives that will serve as suitable tributes to Dr. Wangensteen." As was anticipated, this organization received enthusiastic support. A number of meetings were held, and a fund was established to provide for travel and other educational opportunities for Fellows in surgery at the University. At the annual meeting in 1954 it was agreed that the most appropriate way in which we could further express our gratitude to our teacher would be to present a series of scientific papers, subsequently to be published in SURGERY, on the occasion of his twenty-fifth anniversary.

The preparation of these manuscripts is but a small token of our appreciation, but the scope of the dissertations is perhaps symbolic of the extent of Dr. Wangensteen's influence upon us. For diverse as our current interests are, their origins can all be traced to our fortunate contact with his ideas, his encouragement, and the sheer force of his dynamic spirit.

With unfailing confidence in the surgery of tomorrow, he has given devoted attention to the surgeons of the next generation. While vigorously upholding the best traditions of his art, he has insisted upon subjecting new ideas to fair trial, lest they be dissipated in an atmosphere of tradition and authority. He has devoted his energy to providing opportunities for young surgeons to take their ideas to the laboratory, and through his establishment of the Surgical Forum at the annual congress of the American College of Surgeons, he has provided a podium on which to present their contributions.

With a firm conviction that all sciences are relevant to surgery he has broadened the base of surgical training. Through his own studies of disturbed physiology in intestinal obstruction, peptic ulcer, malignancy, and scores of other surgical situations, he is transforming the empirical craft of the past into the exact science of the future.

Unlike most of the great professors of today, he assumed his position in his University with little inheritance from the past and no lineage of famous teachers preceding him. Thus, singlehandedly he has built a heritage and a tradition of which we, his students, are proud to be a part.

CARDIOJEJUNOPEXY FOR CORONARY ARTERY DISEASE

An Experimental Study

Ivan D. Baronofsky, M.D.,* Donald W. Hannon, M.D., and Charles E. Turback, M.D., Minneapolis, Minn.

(From the Ancker Hospital Surgical Research Laboratory and the Departments of Surgery, Ancker Hospital, St. Paul, Minnesota, and the University of Minnesota)

INTRODUCTION

THE incidence of coronary heart disease is increasing tremendously. The treatment of this disease has been, in general, the prerogative of the internist. We should like to present in this paper some of the results obtained by us in attempts to revascularize the heart by the use of bowel and also to discuss some of the problems inherent in the experimental approach in coronary heart disease. It is not intended to suggest at this time that the future advances in the treatment of coronary heart disease lie within the surgeon's realm, since much has been done by the internist. We feel, however, that the surgical treatment of coronary heart disease may be invoked when medical treatment has failed.

METHODS AND MATERIALS

In dogs, bowel was applied to the heart (cardiojejunopexy) in two stages. At the first operation, through a midline incision, a segment of jejunum or ileum is divided and the distal end closed with interrupted silk sutures. This end is then loosely sutured to the diaphragm. The intestinal continuity is then re-established by means of a Roux Y anastomosis (Fig. 1). The mesentery is closed and then the abdomen is closed. About ten days to two weeks later, the chest is opened through the left sixth intercostal space. A small opening is made in the diaphragm and the segment of intestine is pulled up into the chest. The pericardium is then opened, and the epicardium between the anterior descending and circumflex coronary arteries is stripped. The segment of intestine is sutured to the denuded portion of the heart after the serosa has been stripped off its surface (Fig. 2).

The pericardium is then closed loosely. The intestine is sutured to the diaphragm in order to obliterate any space between the gut and diaphragm. Seventy-eight dogs were prepared in this manner.

In order to study the effectiveness of these procedures, the coronary arteries were occluded in stages by means of a Goldblatt clamp.[1] The total time taken for this staged occlusion was one month. Three groups of prepared animals as well as three groups of controls were studied and compared as to mortality following ligation of each one of the major coronary vessels.

In addition to the above, various other studies which have been or are in the process of being reported were made. Mention will be made of these in the discussion.

This work was supported by grants from the U. S. Public Health Service and the Life Insurance Medical Research Fund.

*At present Dr. Baronofsky is Chief of Thoracic Surgery, U. S. Naval Hospital, San Diego, Calif.

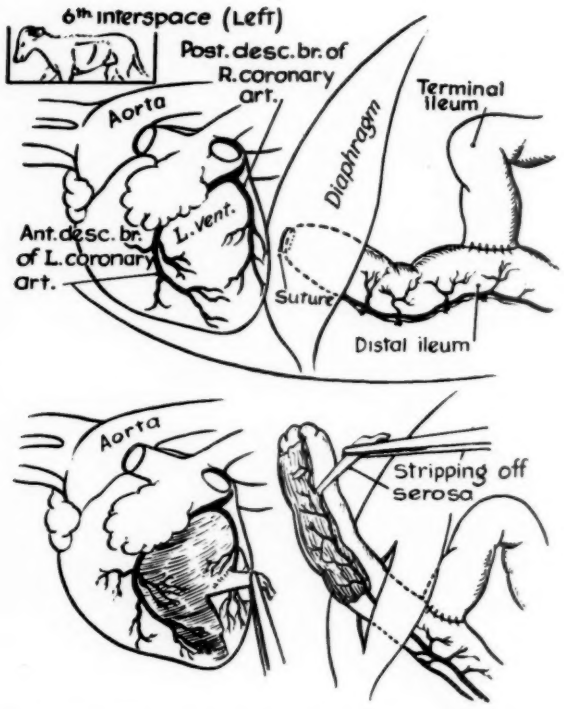

Fig. 1.—First stage in cardiojejunopexy, using the Roux Y method of restoring intestinal continuity.

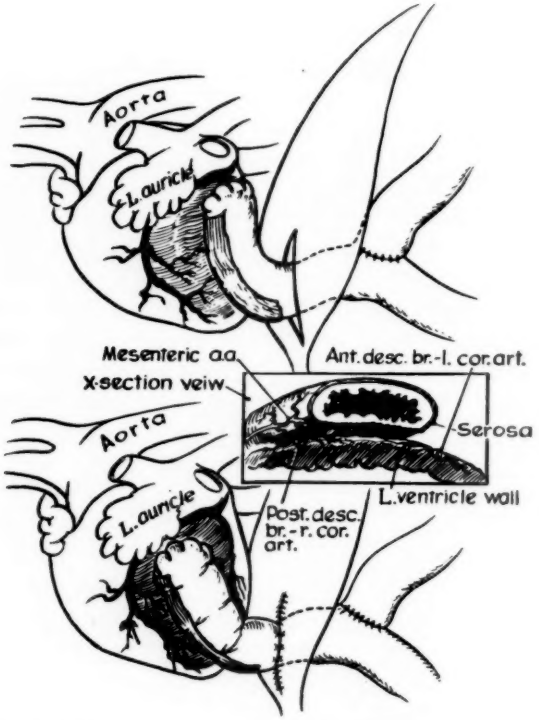

Fig. 2.—Suturing of intestine to heart in second stage of cardiojejunopexy.

RESULTS

The results are summarized in Table I.

TABLE I. MORTALITY RATES OF OCCLUSION OF THE CORONARY ARTERIES IN ANIMALS WITH CARDIOJEJUNOPEXY AND CONTROLS

	NUMBER OF DOGS	DEATHS	MORTALITY RATE (PER CENT)
Anterior Descending Occlusion			
Cardiojejunopexy	20	13	25
Control	20	5	65
Circumflex Artery Occlusion			
Cardiojejunopexy	19	4	21
Control	20	13	65
Right Coronary Artery occlusion			
Cardiojejunopexy	47	5	10
Control	16	5	31

DISCUSSION

As shown above, definite protection was offered to the heart when the bowel was placed upon it. We have previously shown that blood vessels which will allow the passage of barium sulfate particles are present, allowing for communication between the arteries of the bowel and the heart. One of the major problems that we have had has been inability to show consistently by dye injection the directional flow within these vessels.

The protective mechanism of the bowel's presence on the heart is still not entirely clear in our minds. During the course of our experiments, we logically thought that if the mesenteric artery supplying the loop of bowel on the heart were occluded and electrocardiographic changes occurred, some conclusion as to the directional blood flow might be obtained. When this was done, changes occurred only occasionally.

It is our opinion that perhaps the bowel acts as a bridge for vessels coming from other sources (extracoronary vessels) in addition to supplying vessels directly to the coronary artery distal to the occlusion. In addition, it is possible that the intercoronary circulation is greatly stimulated by the presence of bowel.

One of the main problems present in any experimental approach in coronary heart disease is the application of a method to human coronary heart disease. It would appear that the ideal solution to a problem of this sort is the presence of an anatomic and pathologic state in the dog similar to that in the human being. That this is not true is well known. In the first place, the dog's coronary arteries are not completely similar anatomically, nor is coronary heart disease present in the dogs used in the above experiments. It was our feeling that a more closely similar set of pathologic circumstances would prevail in the dog if the coronary arteries were occluded in stages. However, we fully realize the inadequacy. Recently Beck,[2] the pioneer in this field, has suggested a backflow test which he claims is a more accurate method of testing a particular procedure suggested for the treatment of coronary heart disease. This would seem to be a logical procedure and should be used. However, the question of applicability of the results in determining if a particular operation can be done

on the human being still remains to be seen. It would appear that there is some benefit obtained by some of the coronary patients who have been treated surgically by merely opening the pericardial sac. To what this benefit is due remains to be seen.

A test that has appeared useful to us in testing for the efficacy of cardiojejunopexy following occlusion of a coronary vessel is the hypoxia test.[1] In this test, animals are placed on 10 per cent oxygen and electrocardiograms are taken simultaneously. A definite protective action of cardiojejunopexy was shown. This test, incidentally, would be useful in testing for the protective action of other surgical procedures when the experimental animals are used.

Another problem that has come up in the application of the experimental approach to clinical patients has been the localization of the diseased coronary. It would seem that if that vessel could be located, then the segment of bowel could be more properly placed. During the course of our work, we began to make coronary arteriograms and have developed it into a fairly reliable technique.[3] It is, of course, a modification of other proposed techniques. Coronary arteriography should be a very useful adjunct in the diagnosis of coronary heart disease in the human.

SUMMARY AND CONCLUSIONS

1. The mortality rates of a series of animals that had a loop of bowel placed on the heart (cardiojejunopexy) and subsequently had each of the main coronary arteries occluded were compared with controls.

2. Definite protection to the heart was afforded those animals with a cardiojejunopexy.

3. The mechanism of this protection was not clearly defined.

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A PARENCHYMATOUS SURGICAL APPROACH TO THE PROBLEM OF PORTAL HYPERTENSION

DAVITT A. FELDER, M.D., JOHN J. HAGLIN, M.D. (BY INVITATION), AND THOMAS O. MURPHY, M.D. (BY INVITATION), ST. PAUL, MINN.

(From the Surgical Research Laboratory, St. Joseph's Hospital)

ATTEMPTS to relieve portal hypertension by creating extrahepatic channels of return to the heart have been abundantly tested both by nature and by man. To date, none have proved entirely satisfactory. It seemed possible that the liver parenchyma might be used as a means of return of portal venous blood and the spleen appeared to be a latent path of outflow from the portal venous bed. The parenchyma of the liver fused with the parenchyma of the spleen should provide at least a great potential of vascular connections.

We began to explore the feasibility of such a procedure in rabbits and a technique of fusing the spleen to the liver was developed. Included in this report are the early results of the application of such a fusion to the problem of portal hypertension.

METHOD

The rabbit is anesthetized with intravenous Nembutal. An endotracheal tube is inserted and attached to a respirator.

The abdomen is opened and the vasa brevia of the spleen are transected and ligated. A nonerushing clamp is placed across the splenic pedicle to control bleeding during the fusion. The capsule and some parenchyma are removed from about 85 per cent of the anterior portion of the spleen, leaving a raw surface. Liver capsule and parenchyma are excised from the left lobe, creating a raw bleeding surface of corresponding size. The raw parenchymal surfaces of liver and spleen are approximated and held together by a continuous anterior and posterior row of 6-0 silk suture. Care is taken to place the sutures deeply in order to obliterate dead space.

The portal vein in the rabbit divides into a right and left branch. The right branch drains into the caudate lobe and the left branch into the right and left lobes of the liver. Taking advantage of this anatomical arrangement, our experiments have been divided into the following groups: Controls, (A) total portal vein ligation, (B) staged ligation of left and right portal veins; Group I, splenohepatic fusion followed by total portal vein ligation; Group II, splenohepatic fusion followed by left portal vein and later total portal vein ligation; Group III, splenohepatic fusion followed by right portal vein and later total portal vein ligation; Group IV, simultaneous splenohepatic fusion and right portal vein ligation.

RESULTS

Controls.—(A) In a group of 20 animals the portal vein was ligated on the hepatic side of its last tributary (total portal vein ligation). This resulted in the death of all of the animals from shock and hemorrhage into the bowel within three hours after the ligation.

(B) In another series of ten animals the left and right portal veins were ligated at six-week intervals. All of these animals succumbed within three hours after the second ligation.

Group I.—A splenohepatic fusion was carried out in 10 rabbits. Six weeks after this a total ligation of the portal vein resulted in the death of all of these animals in from three to eighteen hours with a mean survival time of nine hours. Examination of the splenohepatic fusions in these animals by the vinyl acetate injection and digestion technique showed definite splenohepatic vascular pathways (Figs. 1*A* and 1*B*).

Group II.—Six weeks after splenohepatic fusion, the left branch of the portal vein was ligated in 18 animals. Sixteen of these animals were then subjected to a total portal vein ligation as a second stage after another six weeks. Four out of these 16 animals are alive to date. Those animals which succumbed after the second stage procedure had a mean survival time of twenty-eight hours.

After ligation of the left branch of the portal vein the left and right lobes of the liver became atrophic and the caudate lobe hypertrophied. The splenohepatic fusion (made with the left lobe) became correspondingly decreased in size.

Fig. 1*A*.—Splenohepatic fusion in rabbit. S = Spleen, L = Liver.

Group III.—To date, 3 rabbits with splenohepatic fusion have had a first stage right branch ligation followed by a total portal vein ligation after six weeks. Of these, one animal survived. This experiment is still in progress.

Group IV.—In this group of animals a right portal vein ligation and splenohepatic fusion are being performed at the same operation. Of the 8 such animals studied so far, 4 have survived.

The following liver function studies were done in these animals: total protein, van den Bergh, cephalin flocculation, thymol turbidity, prothrombin time, alkaline phosphatase, and Bromsulphalein determinations. In all animals except those surviving total portal vein occlusion, these tests were normal. In the latter group of animals some impaired function was indicated.

Histologic studies six weeks after splenohepatic fusion show blood vessels and minimal scar tissue in the line of fusion (Fig. 2). No significant hematomas have been found.

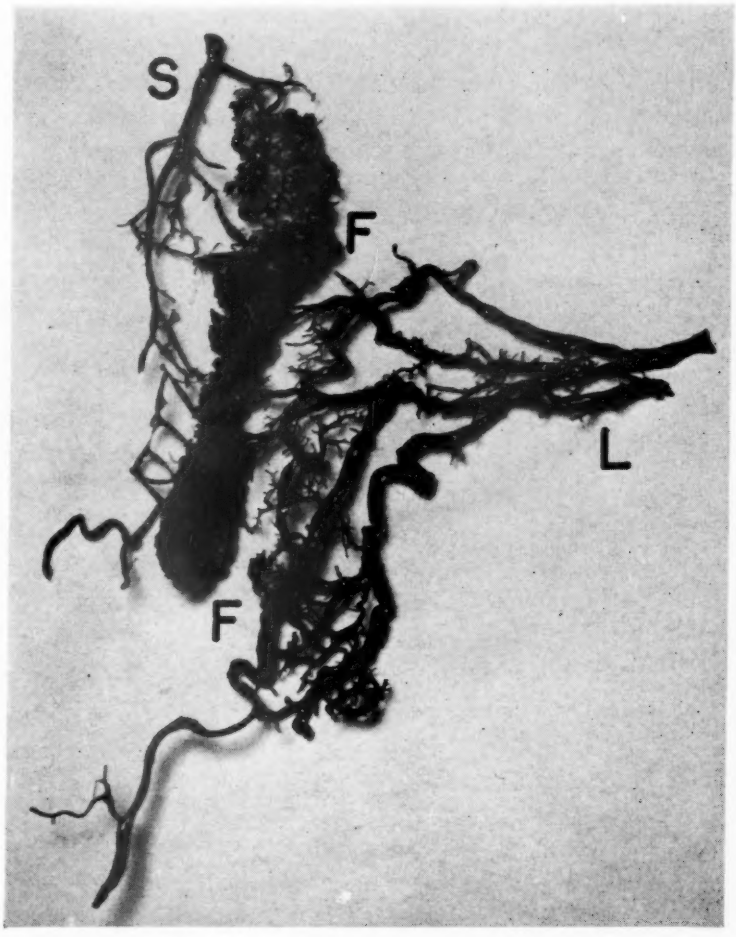

Fig. 1B.—Splenohepatic vascular pathways demonstrated by vinyl acetate injection. S = Spleen, L = Liver, F-F = line of fusion.

DISCUSSION

It is noteworthy that following splenohepatic fusion and total ligation of the portal vein (Group I), the animals lived appreciably longer than those in the control group. It is of further significance that after left portal vein ligation and resultant atrophy of the fused lobe, and after subsequent total portal vein occlusion (Group II), the mean survival time was appreciably prolonged and 25 per cent of the animals have survived. In the control group without splenohepatic fusion all of the animals died. Splenohepatic fusion apparently protects the rabbits against the results of acute total portal vein occlusion. It can be presumed that the new splenohepatic channels afford a significant outflow for the portal venous blood even though it is inadequate.

The experiments in Group III and Group IV were begun after we observed consistent atrophy, after eight to ten weeks, in the right and left lobes of the liver following left portal vein ligation. It is possible that, after a first stage ligation of the right portal vein, and resultant hypertrophy of the left lobe, and possibly concomitant increased function of the splenohepatic fusion, a significantly higher survival will result.

In those animals having simultaneous right branch portal vein ligation and splenohepatic fusion we hope to have increased the flow of portal venous blood in the direction of the fusion and to have protected the parenchyma of the left lobe by allowing its venous drainage to remain intact. This latter procedure would also obviate one of the many operations.

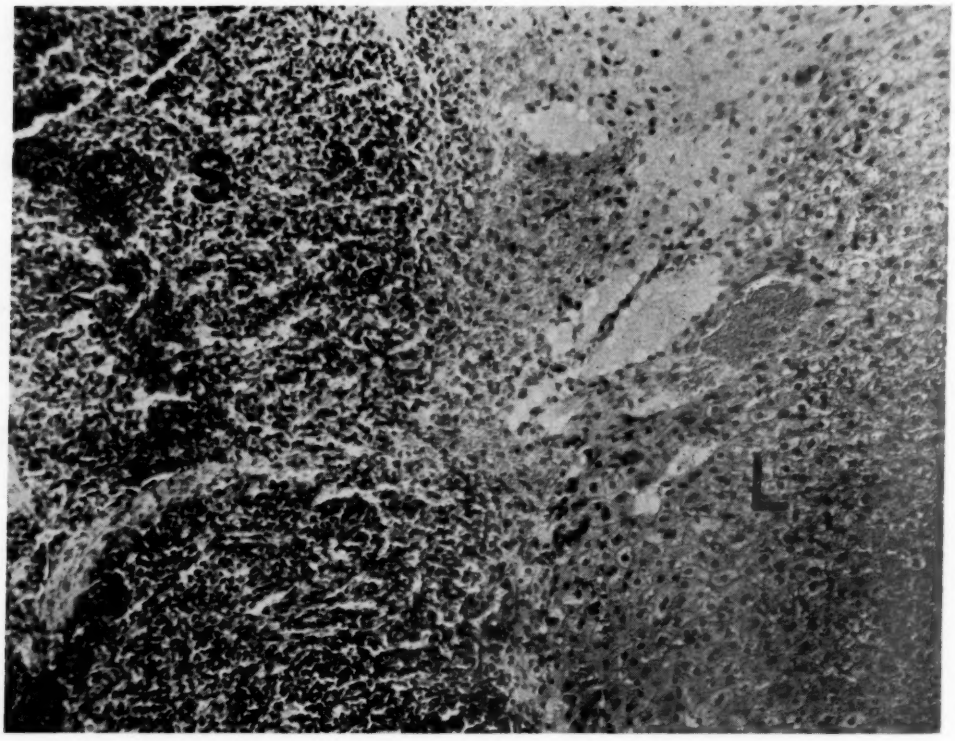

Fig. 2.—Photomicrograph showing line of fusion between spleen (S) and liver (L).

In spite of what might be expected, there has been only moderate blood loss during or after the fusion. This has been mainly from the cut surface of the liver. However, it is remarkable that late hemorrhage and hematomas have not resulted. We believe that an important factor in a satisfactory anastomosis is the removal of enough splenic pulp to relieve tension on the edge of the capsule. This allows for a better approximation which diminishes blood loss.

It is possible that, even in a cirrhotic liver, portal venous blood passing through the sinusoids from a splenohepatic fusion may be metabolized and detoxified by liver cells. In portal cirrhosis and hypertension one would expect the blood to flow from the spleen toward the central veins since this would

represent the path of least resistance. Such a procedure of splenohepatic fusion might then have an application to instances of intra- as well as extrahepatic portal vein obstruction.

We are also investigating the applicability of this procedure in dogs. It is already apparent that in this animal our problems will be different than in the rabbit. However, we have found that the technical procedure of splenohepatic fusion can be satisfactorily accomplished in this larger animal.

SUMMARY

A technique of splenohepatic fusion has been developed in rabbits. This fusion appears to afford a significant protection against early death after total portal vein occlusion.

A STUDY OF THE GENESIS OF SHOCK ASSOCIATED WITH EXPERIMENTALLY INDUCED HEPATIC NECROSIS IN DOGS

DAVID STATE, M.D., AND IRVING LICHTENSTEIN, M.D. (BY INVITATION),
LOS ANGELES, CALIF.

(From the Department of Surgery, Cedars of Lebanon Hospital and University of Southern California, Medical School)

THE association of liver necrosis and shock has long been known. The exact mechanisms involved, however, are not understood. The term "hepatorenal syndrome" has been applied to the clinical entity to cover this ignorance, for usually there is suppression of urine formation. Shorr and Zweifach[1] believed that a vasodepressor substance called V.D.M., liberated by the hypoxic liver, was responsible, while Markowitz and co-workers[2] have stressed the importance of a bacterial factor, originating in the damaged liver. In previous experiments carried out in 1951, Rauch, Muller, and State[3] felt that shock associated with a damaged liver was due to the trapping of blood in the portal system, resulting in a severe reduction of effective circulating blood volume.

In an effort to obtain more light on the problem, experiments were devised to evaluate the following possible factors in the production of shock associated with hepatic necrosis; (1) pooling of blood in the portal circulation, (2) elaboration of a vasodepressor substance similar to V.D.M., (3) production of a bacterial factor, and (4) decrease in effective circulating blood volume due to hemorrhage into the hypoxic liver.

METHOD

1. Evaluation of Pooling of Blood in the Portal System.—Experiments were carried out on healthy mongrel dogs. Using aseptic technique and under sodium pentobarbital anesthesia (15 mg. per pound body weight) the abdomen was opened in the midline. Plastic catheters were placed in the portal veins and femoral vein and artery to obtain continuous pressure readings in each of these vessels. Care was taken to prevent overexposure of the bowel and manipulations of the intestine and mesentery were kept to a minimum. After pressures in the portal vein and femoral artery and vein had remained steady for one hour, liver necrosis was induced in one group of dogs by the intraportal injection of carbon tetrachloride (2 c.c. per 10 pounds body weight). In a second series of dogs, a portacaval shunt was made by anastomosing the portal vein and inferior vena cava side to side and ligating the portal vein distal to the anastomosis. Carbon tetrachloride (12 c.c. per 10 pounds body weight) was then injected slowly into the portal vein proximal to the ligature.

Series I: (Fig. 1.) Following the injection of carbon tetrachloride into the portal vein the following observations were noted: (1) marked swelling and hemorrhagic necrosis of the liver; (2) immediate rise in portal venous pressure from an average of 8 to 22 cm. of water—this pressure remaining high until death occurred; (3) precipitous drop of systemic arterial pressure to "shock" levels (below 75 mm. Hg)—the drop in blood pressure slowly progressing until death supervened.

Series II: (Fig. 2.) In the dogs with an Eck fistula, after the injection of carbon tetrachloride into the portal vein proximal to the ligature, the following changes occurred: (1) a marked sudden drop in systemic arterial pressure to below 30 mm Hg, the animal sur-

Supported in part by a grant from the U. S. Public Health Service—#H-2210.

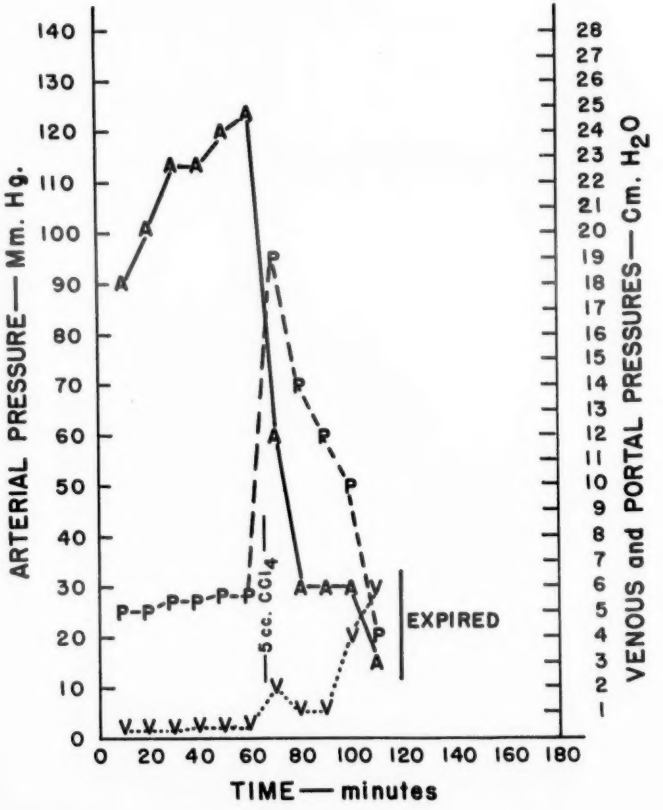

Fig. 1.

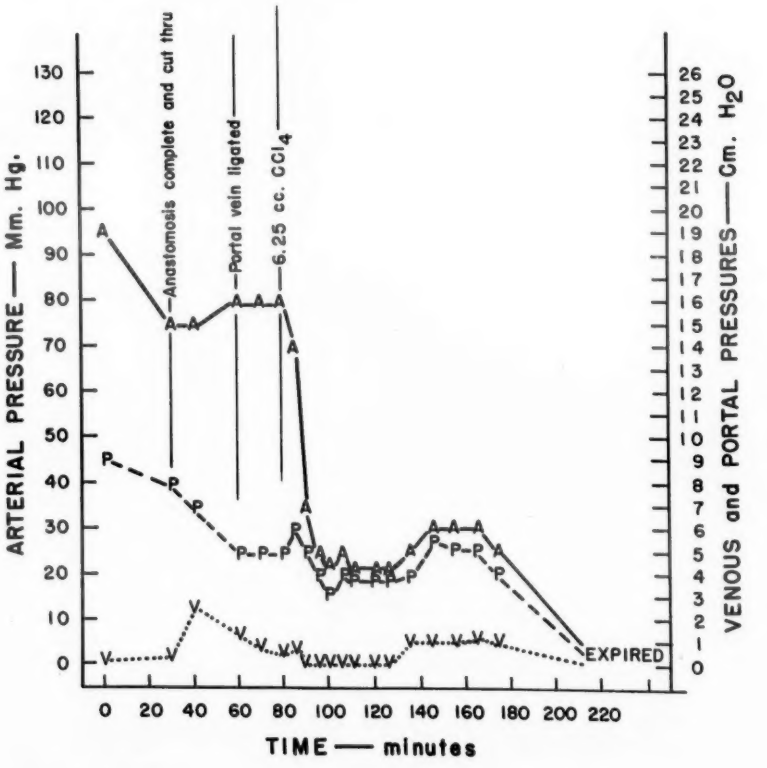

Fig. 2.

Fig. 1.—Following the injection of carbon tetrachloride into the portal vein, there is a marked elevation of portal venous pressure, sudden decrease of systemic arterial pressure to "shock" level. The systemic venous pressure rises slightly terminally.

Fig. 2.—After an Eck fistula has been made, the injection of carbon tetrachloride into the portal vein results in a sudden drop in systemic arterial pressure to "shock" levels, in spite of absence of an increased portal venous pressure. These animals survived longer than those without a portacaval shunt.

viving, however, for over a period of 120 minutes; (2) a slight drop in portal venous pressure from 8 to 4 cm. water until death occurred, when the pressure dropped to 0 cm.; (3) no significant change in systemic venous pressure; (4) a marked engorgement and necrosis of the liver.

Diversion of the portal blood into the inferior vena cava prevented the marked elevation of portal pressure, following the intraportal injection of carbon tetrachloride, but it did not prevent the sudden onset of severe persistent hypotension ending in the death of the animal. The animals with portacaval shunts, however, survived longer than those without shunts.

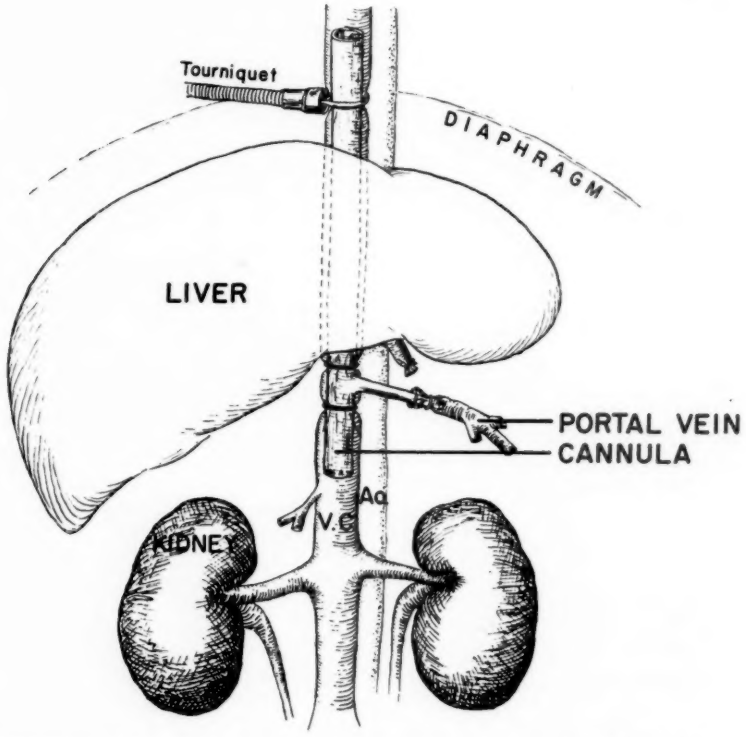

Fig. 3.—Technique for producing prolonged hypoxia and reversible exclusion of the liver. An Eck fistula is made by use of a silicone-lined plastic cannula. The vertical limb is inserted into the transected portal vein. The proximal portion of the horizontal limb extends into the inferior vena cava proximal to the insertion of the hepatic veins. A tourniquet at this level occludes hepatic venous return but does not interfere with the flow in the inferior vena cava. Not shown is the hepatic artery which is tied in continuity near its origin and a clamp also placed across the porta hepatis at the hilum of the liver. With the portal blood shunted into the inferior vena cava, the arterial inflow obstructed and the hepatic veins occluded, the liver can be made hypoxic for long periods of time. The effects of returning the damaged liver to the circulation by releasing the tourniquet about the hepatic veins, and arterial inflow can then be noted.

In order to evaluate the other possible causative factors in the production of shock following liver necrosis, it was necessary to produce liver necrosis by some other means than intraportal injection of carbon tetrachloride. To answer this need, we have developed the following technique which permits us to exclude all blood flow to the liver in situ for a given period, thus producing liver necrosis by severe prolonged hypoxia. Raffucci and Wangensteen[4] showed that total inflow occlusion to the liver in normothermic animals for one hour was uniformly fatal in dogs. Bernhard and co-workers[5] confirmed these observations.

Using a silicone-lined plastic T tube,* an Eck fistula was made as described by LeVeen[6] (Fig. 3). The proximal horizontal limb of the T tube which was inserted into the inferior vena cava reached above the level of the entrance of the hepatic veins, so that a tourniquet

*Kindly furnished us by Dr. Harry H. LeVeen.

placed around the inferior vena cava, just proximal to the hepatic veins, occluded them, without obstructing the flow in the inferior vena cava. This maneuver was necessary since it is virtually impossible to occlude the hepatic veins separately. The cessation of arterial inflow to the liver was accomplished by placing a ligature around the main hepatic artery near its origin from the celiac axis, clamping the portal hilum near the liver and mobilizing the liver completely from the diaphragm, stomach, and duodenum. With the portal blood flow deviated into the inferior vena cava, the arterial inflow completely occluded, and the hepatic venous outflow totally obstructed, the liver is excluded from the body's circulation, even though it remains in situ.

With all this experimental preparation, an evaluation of the following factors was carried out:

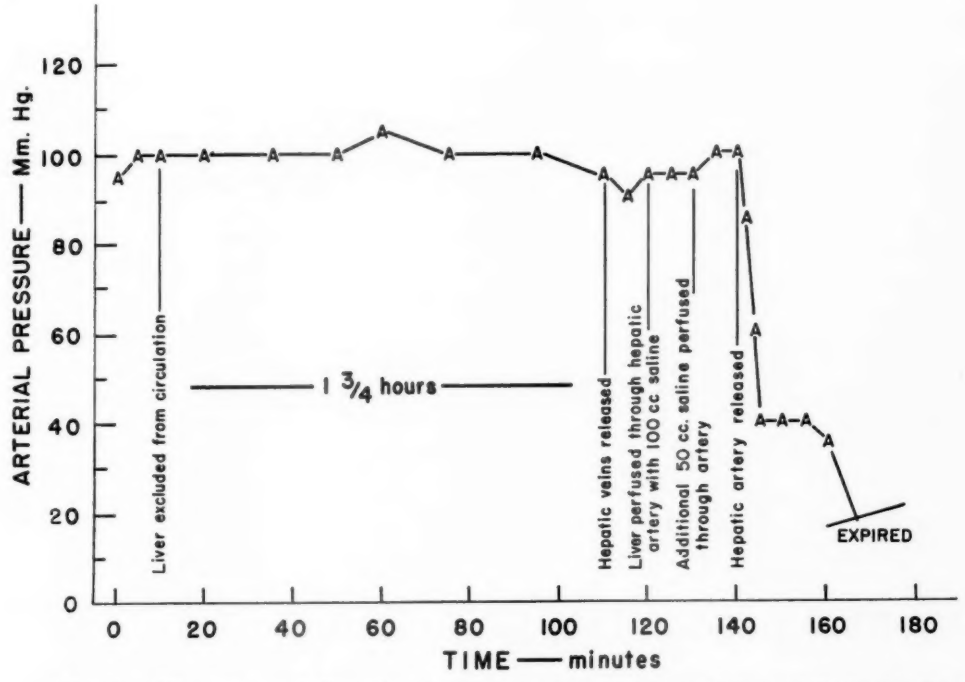

Fig. 4.—After one and three-fourths hours of hypoxia, perfusion of the liver with saline through the hepatic artery fails to alter systemic arterial pressure. The dogs were given penicillin G 400,000 units and 0.5 Gm. dihydrostreptomycin for three days prior to the experiment. Once the hepatic artery is released, "shock" and death occur rather quickly.

2. The Elaboration of a Toxic V.D.M.-Like Substance From the Damaged Liver.—Dogs were placed on combiotics (400,000 units penicillin G and 0.5 Gm. dihydrostreptomycin) for approximately three days before the experiment was carried out. In the manner described above, the occlusion of blood flow to the liver was carried out for one and three-fourths hour. At the end of this time, the ligature about the hepatic veins was released and the liver perfused with 100 c.c. of 5 per cent glucose in saline solution through the portal vein containing identifying methylene blue. Samples of blood were drawn from the right atrium to determine the presence of methylene blue and establish the fact that the perfusion fluid had passed through the liver. An additional series of dogs were perfused with saline solution through the hepatic artery.

During the period the liver was hypoxic but excluded from the circulation (one and three-fourths hours no change in systemic arterial pressure was noted. Following the release of the tourniquet about the hepatic vein a slight temporary drop of blood pressure occurred. No change was noted when the liver was perfused with saline solution either through the portal vein or hepatic artery. Following the release of the hepatic artery, however, severe hypotension and death occurred (Figs. 4 and 5).

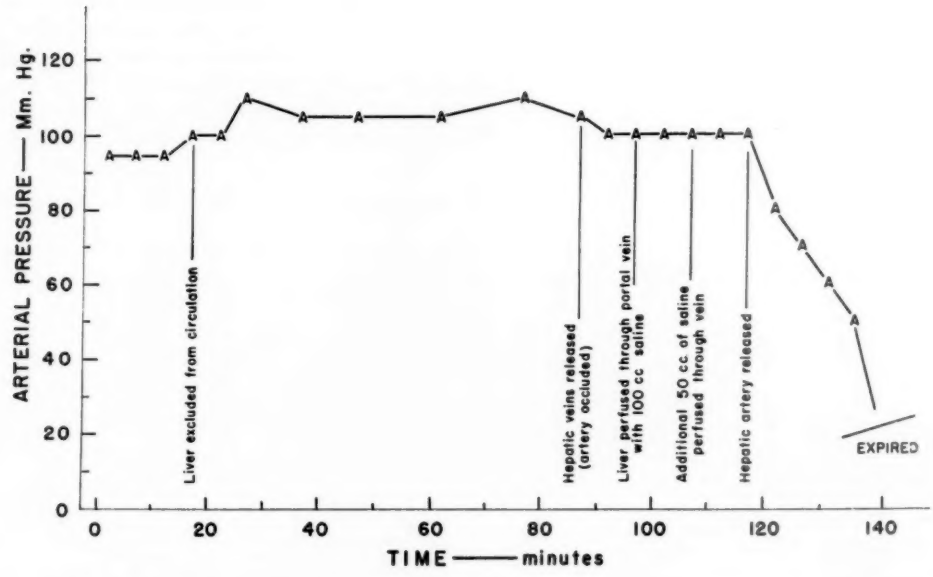

Fig. 5.—The liver was rendered hypoxic for approximately one hour. Perfusion of the liver through the portal vein circuit caused no significant change in systemic arterial pressure. The animals were not prepared with antibiotics. Note again the sudden drop of arterial pressure following the release of the hepatic artery.

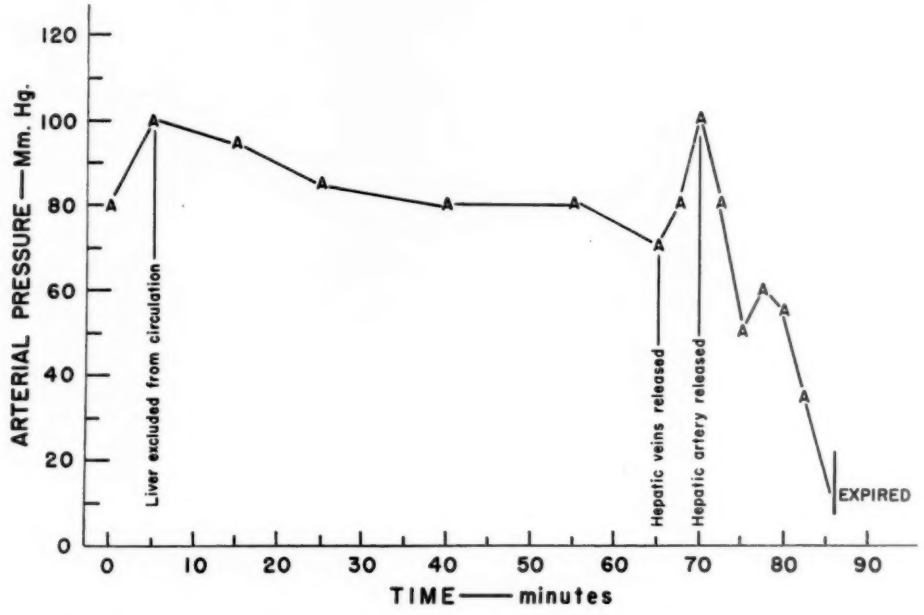

Fig. 6.—The liver was excluded from the circulation for approximately one hour. On releasing the hepatic vein tourniquet a slight drop of arterial pressure occurred followed by a rise. Once the hepatic artery was released, the liver became enlarged and hemorrhagic, the dog developed severe hypotension, and expired within fifteen minutes.

3. The Significance of a Bacterial Factor.—In an effort to determine the role of a bacterial factor in the production of shock and death in our animals, this series of dogs were handled the same as *2* above, except no antibiotics were given before experiments were carried out.

Perfusion of the hypoxic liver in the animal not receiving antibiotics does not differ from that seen in animals pretreated with the antibiotics. No significant change in systemic arterial pressure occurred during or following the perfusion of the liver. Hypotension and death occurred only following the restoration of hepatic artery blood flow (Fig. 5).

4. Factor of Local Blood Loss in the Hypoxic Liver.—In this group of dogs total vascular occlusion of the liver for one hour was carried out as previously described. Multiple biopsies of the liver were taken during and following the period of occlusion. The ligature about the hepatic vein was released first, and then the hepatic inflow was restabilized by removing the ligature about the main stem and removing the clamp from the porta hepatis.

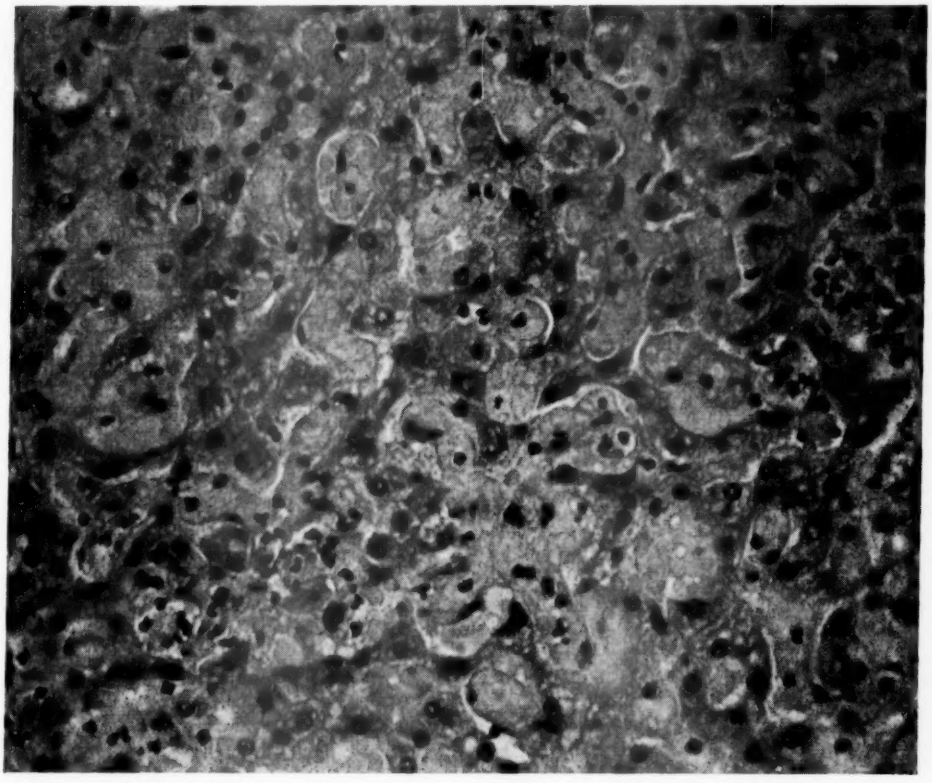

Fig. 7.—Microscopic section of liver following a period of one and three-fourths hours of hypoxia, followed by release of obstructions to hepatic veins and arterial inflow. Biopsy was taken approximately ten minutes after restoration of circulation. Note swelling and necrosis of liver cells and marked congestion of liver sinusoids. (×360.)

As noted from previous experiments there was little change in arterial pressure during the time the inflow occlusion was carried out. Following the release of the tourniquet about the hepatic veins, a slight drop followed by a rise in arterial pressure occurred. At this stage release of the hepatic artery inflow was followed by a sudden drop of arterial pressure, with death of the animal within a period of fifteen to twenty minutes. A comparison with Figs. 4 and 5 shows the same findings following the return of hepatic artery flow to the damaged liver (Fig. 6).

The liver became markedly engorged following the return of hepatic artery flow, and histologic pictures of the liver, at this time, show necrosis of liver cells and marked engorgement of the liver sinusoids (Fig. 7).

DISCUSSION

Severe persistent hypotension following severe damage of the liver, produced by cytoxic agents (such as carbon tetrachloride) or prolonged hypoxia, is quite readily reproducible in the dog. The picture is distinctly different from that described by Markowitz[7] after ligation of the hepatic artery. In his dogs death resulted in from twenty-four to forty-eight hours during which time the animal developed hepatic coma or semicoma. At autopsy the liver was transformed into "a large, stinking, mushy organ," which, on histologic examination, showed extensive destruction of the liver parenchyma and great numbers of anerobic rods. The counterpart clinical picture is one seen after accidental ligation of the hepatic artery in biliary tract surgery with inadequate collateral circulation. The problem we were interested in studying primarily was the effect of prolonged interruption of afferent blood flow to the liver, such as one might encounter in controlling bleeding from the liver during removal of large portions of that organ. Raffucci and Wangensteen,[4] investigating this problem, found that twenty minutes was the maximal period of continuous occlusion of the hepatic artery and portal vein that could be tolerated. All of 39 animals with afferent occlusion for one hour died. They also noted a great drop in systemic arterial pressure in all of their experiments.

In analyzing possible etiologic factors for the severe hypotension and death, we first considered the factor of sequestration of blood in the gastrointestinal vascular bed. In previous experiments[3] we had noted a marked rise in portal venous pressure and a precipitous drop in systemic pressure following liver necrosis produced in dogs by the intraportal injection of carbon tetrachloride. The very fact, however, that shunting all of the portal blood into the systemic circulation by a portacaval anastomosis when liver necrosis was produced by prolonged hypoxia did not protect the dog from severe hypotension and death would indicate that some other mechanism must be responsible. These animals, however, survived longer than those that did not have an Eck fistula. The decreased length of survival in dogs without portal caval shunts may be related to the sequestration of blood in the portal system, and the prevention of this factor by clamping off the arterial inflow to the gut, as recommended by Raffucci and Wangensteen,[4] is of great importance.

Turning to a consideration of other possible causative factors, the elaboration of a vasodilator material (V.D.M.) was considered. Shorr and his coworkers[1] have demonstrated the presence of V.D.M. in the circulation, during hypovolemic shock. It was thought that this substance was manufactured in the hypoxic liver. In liver slices incubated in either serum or Kreb's bicarbonate medium, in an atmosphere of 95 per cent N_2 and 5 per cent CO_2, no V.D.M. was produced for twenty to thirty minutes, but from then on, it was produced in increasing quantities. In an excellent review of the subject, Granick[8] points out that V.D.M. is probably ferritin, an iron protein compound made up of a protein "apoferritin" and an iron-containing portion ($Fe\ OOH_8$. $Fe\ OPQ_3\ H_2$) firmly bound to the protein. Although Chambers and associates[9]

reported that the blood of animals in the terminal stages of shock contained V.D.M., when this material was injected into the rat it did not lower the blood pressure in shock. The observations we have made on the innocuous character of the perfusate of the liver made anoxic, for a period of as long as one and three-fourths hours, would indicate that V.D.M. is not produced in the hypoxic liver, or, if it is, it has no effect on the blood pressure. Studies are being undertaken in our laboratory to determine how much, if any, V.D.M. can be perfused from the hypoxic liver.

Rappaport and Markowitz[10] have shown how extensively anerobic bacteria multiply in the liver after ligation of the hepatic artery. It is unlikely that the bacterial factor plays a significant role in our experiments. Sufficient time did not elapse to permit significant growth of anerobes in the liver of our dogs. The perfusate of the liver, after one hour of afferent inflow occlusion, was not "toxic," and whether the animals had or had not received large doses of antibiotics prior to liver damage made no difference. The significance of the "bacterial factor" in man is also open to question, for unlike dogs, most bacteriologic studies made on human beings shows the liver to be free of organisms.[11]

The factor of blood loss into the hypoxic liver appears to be the most significant one in our studies.

It is evident that after total occlusion of blood flow to the liver for one hour, when the hepatic artery is released the liver becomes enlarged and hemorrhagic. Within a few minutes, the blood pressure drops severely. Histologic section shows cellular destruction and marked congestion of all sinusoids. How much blood is lost into the liver and whether it is sufficient to decrease effective circulating blood volume are problems for which we are hoping to find answers by continued experimentation. From studies done by Grindlay, Herrick, and Mann[12] it is known that as much as 163 c.c. per minute may flow into the liver through the hepatic artery. If most of this were sequestrated into the liver, it can readily be seen that within a short time sufficient blood could be lost to explain shock on the basis of a rapid decrease in effective circulating blood volume.

Why blood is sequestrated in the damaged liver is not entirely known, but it may be related to damage of vascular endothelium, disruption and blockage of the normal intrahepatic vascular tree by swollen, damaged cells and necrotic debris.

From the therapeutic point of view, these studies would point to the need of maintaining liver and endothelial cell integrity whenever total inflow occlusion of the liver is indicated. Raffucci[4] has recommended intermittent occlusion allowing a thirty-minute rest between two fifteen-minute occlusion periods. Bernhard[5] recently has shown that hypothermia protects the dog liver with total inflow occlusion for one hour. This may be a valuable adjunct to be tried in man. From our studies it is apparent that repeated blood transfusions in an effort to maintain effective circulating blood volume are also in order.

SUMMARY AND CONCLUSIONS

1. An experimental approach to acute hepatic necrosis is described.

2. Severe persistent hypotension progressing to death is uniformly seen in dogs with hepatic necrosis.

3. The possible etiologic factors considered and studied were: (a) sequestration of blood in the portal system; (b) elaboration of V.D.M. by the damaged liver; (c) production of a bacterial factor; (d) decrease in effective circulating blood volume by hemorrhage into the liver from the hepatic artery. Initial preliminary studies would point to the last-mentioned factor as being most significant.

4. The practical implications of these studies, as pertains to therapeutic problems necessitating prolonged vascular inflow occlusion to the liver, are discussed.

The authors would like to acknowledge the aid given by Dr. Nathan Friedman, Department of Pathology, Cedars of Lebanon Hospital, in interpreting the histologic sections in this report.

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THE MYENTERIC PLEXUS OF THE PYLORUS: ITS EARLY NORMAL DEVELOPMENT AND ITS CHANGES IN HYPERTROPHIC PYLORIC STENOSIS

STANLEY R. FRIESEN, M.D., JAMES O. BOLEY, M.D., AND DON R. MILLER, M.D.,
KANSAS CITY, KAN.

(From the Departments of Surgery and Pathology and Oncology, University of Kansas School of Medicine)

IT IS interesting that the etiology of hypertrophic pyloric stenosis in infants should remain an enigma for such a long time. This condition was first described by Hirschsprung in 1888.[6] Although the diagnosis and management of infants with hypertrophic pyloric stenosis are well known, the theories of its etiology are obscure and diverse. The peculiarities of the typical clinical course of this condition are explained only theoretically at the present time. The onset of symptoms, for instance, in an apparently normal infant, days or weeks after birth, is not understood. There have been instances of normal-appearing pyloruses examined by roentgenogram[10] and by surgical exploration[9] prior to the development of complete clinical findings of hypertrophic pyloric stenosis a short period of time later. Is there a congenital defect which does not manifest itself at birth? Is there a familial or inherited tendency as suggested in reports concerning the occurrence of hypertrophic pyloric stenosis in families[5] and in monovular twins?[11] The pyloric hypertrophy persists into adulthood when the treatment has been gastroenterostomy (instead of pyloromyotomy) during infancy[2]; the tumor has been reported to disappear, concomitant with the symptoms, when the usual pyloromyotomy has been done.[13]

Halbertsma,[5] in 1936, believed that the congenital and inherited abnormality in these infants consisted of spasm of the pylorus prior to the development of "work hypertrophy" of the pyloric musculature, a secondary feature causing obstructive stenosis. He stated that there is an abnormal length of the pyloric canal (6 mm. or more), indicative of spasm as seen on roentgenologic examination before muscle hypertrophy occurs. He added that the early pylorospasm does not produce symptoms due to the fact that only small quantities of food are given the infant during its neonatal period.

Abnormalities of the myenteric plexuses of the hypertrophic pylorus in infants and adults have been reported.[1, 3] The plexuses lie between the inner circular and the outer longitudinal muscle layers of the pylorus and are controlled by fibers, along the gastroduodenal artery, from the hepatic branch of the anterior vagus nerve.[8]

Little is known of the development of the gastrointestinal nerve plexuses in the human fetus. Yanase,[14] in a study of human fetuses, did not observe peristalsis before the eleventh week although the longitudinal muscle and its nerves had been present since the seventh week. The human fetus can swallow at least as early as the fifth month, perhaps earlier.[12]

In an excellent study Belding and Kernohan[3] report the microscopic findings of the pylorus, both normal and with hypertrophic pyloric stenosis, in infants and adults. In 8 infants with hypertrophic pyloric stenosis there was a definite decrease from normal in the number of ganglion cells and nerve fibers at the pylorus with no significant alteration from normal above or below the pylorus. The cellular structure of the ganglion cells at the pylorus was abnormal in that the "cytoplasm appeared to be disintegrating," with "indistinct nuclear membrane" and segmentation of the nucleolus. Alarotu and Christensen[1] studied 29 autopsied pyloric stenosis cases and reported that "all the specimens showed disorganization in the structure of the ganglia with glia proliferation varying in intensity and degeneration of the nerve cells with shrinkage of the protoplasm as well as of the nuclei."

The theories relating to neuromuscular imbalance and work hypertrophy of pyloric muscle as causes of hypertrophic pyloric stenosis explain some of the peculiarities of the condition. It remains to be shown, however, whether the "nerve imbalance" and the reported ganglion cell changes are caused by failures of embryologic development or abnormal nerve influences, or are secondary to muscle hypertrophy and spasm. In order to learn something about the development of the myenteric plexus of the normal pylorus of the fetus and the infant and also to correlate that information with the findings in pyloric tissue obtained as biopsies from living infants with hypertrophic pyloric stenosis, the following investigation was begun in April, 1952.

METHOD OF STUDY

Surgical biopsy of the pyloric musculature of 18 infants with hypertrophic pyloric stenosis was done for histologic study of the myenteric plexus. The surgical procedure consisted of excision of pyloric tissue, except mucosa, between two parallel longitudinal Fredet-Ramstedt incisions. The excised tissue usually measured 3.0 by 0.3 by 0.3 cm. In addition, the pylorus of one infant who died with hypertrophic pyloric stenosis was obtained by autopsy for histologic study.

To investigate the anatomical development of the myenteric plexuses of the normal pylorus of the fetus and infant, pyloruses obtained at autopsy of stillbirths, premature infants, and full-term infants dying of causes other than hypertrophic pyloric stenosis were studied. The normal pyloruses of infants of an age group similar to those with hypertrophic pyloric stenosis were used as the control group.

Longitudinal tissue sections were employed in all groups of pyloruses for uniformity of observation. Tissue obtained at operation or autopsy was formalin fixed. In some instances the surgical biopsy specimens were fixed in Zenker's solution. The sections were cut at a thickness of 5 μ and at least 2 of the serial sections were closely analyzed from each specimen. Tissue staining was done using hematoxylin and eosin. It was found early in the study that special nerve staining, being more difficult, did not yield sufficient additional information within the range of this study. Although the histologic findings were observed by various members of the surgical and surgical pathology staff of this hospital, the material was graded by one and the same observer for uniformity of data. Pertinent data were obtained relative to (1) the general appearance of the myenteric layer, (2) the number and arrangement of the nests or plexuses of cells per low-power microscopic field (1.55 mm.), (3) the histologic appearance of the ganglion cells and their number per plexus, and (4) the general appearance of the musculature of the pylorus.

RESULTS

The Normal Pylorus of the Human Fetus, Premature Infant, and Full-term Infant (Table I).—The myenteric nerve layer of the pylorus of the fetus at 12 weeks' gestation appears as almost a continuous layer of immature nerve cells with little, if any, segmentation into nests or plexuses (Fig. 1). The cells

TABLE I.—MYENTERIC PLEXUS OF THE NORMAL PYLORUS IN THE HUMAN FETUS, PREMATURE INFANT, AND FULL-TERM INFANT

NUMBER	NAME	SEX	AGE	NO. PLEXUSES PER LOW-POWER FIELD (1.55 MM.)	NO. OF GANGLION CELLS PER PLEXUS ACCORDING TO DIFFERENTIATION§				CAUSE OF DEATH
					0	+	++	+++	
1.	J. F.		12 weeks F*	Continuous	45	0	0	0	Unknown
2.	M. M.		14 weeks F	Tendency to elongated nests	47	0	0	0	Unknown
3.	A. F.		16 weeks F	Elongated nests	49	0	0	0	Unknown
4.	E. D.		16 weeks F	4-6	56	1	0	0	Unknown
5.	B. B. H.	M	24 weeks F	3-5	35	2	0	0	Unknown
6.	B. B. M.	M	26 weeks PI†	3-4	64	5	0	0	Unknown
7.	B. B.	M	32 weeks PI	2-3	90	11	0	0	Subarachnoid hemorrhage
8.	B. B. P.	M	32 weeks PI	2-3	80	9	0	0	Subarachnoid hemorrhage
9.	B. G. D.	F	1 day NB‡	2	31	5	0	0	Atelectasis
10.	M. H.	F	2 days	4	22	7	0	0	Erythroblastosis
11.	J. D. J.	M	3 days	2-5	37	13	0	0	Tracheoesophageal fistula
12.	B. B.	M	3 days	1-3	48	11	1	0	Imperforate anus; patent ductus arteriosus
13.	K. J.	M	6 days	2-4	24	5	0	0	Meningitis
14.	S. K.	M	9 days	3-5	28	8	0	0	Tracheoesophageal fistula
15.	B. B. H.	M	9 days	3-5	27	10	0	0	Atelectasis
16.	R. D.	M	11 days	2-4	58	16	1	0	Ileal atresia
17.	B. G. G.	F	16 days	2-4	25	7	2	0	Teratoma
18.	J. T.	M	30 days	1-3	10	8	7	3	Jejunal atresia; aspiration pneumonia
19.	K. K.	M	60 days	2-4	12	21	0	1	Bilateral bronchopneumonia
20.	G. S.	M	63 days	1-3	7	26	1	3	Hirschsprung's Disease
21.	H. E. St. J.	M	90 days	4	0	19	3	1	Fibroelastosis
22.	G. H.	M	120 days	1-3	2	10	8	2	Hepatic cirrhosis
23.	P. H. F.	F	150 days	2-4	5	14	3	3	Bronchopneumonia

* = Fetus in weeks' gestation.
†PI = Premature infant in weeks' gestation.
‡NB = Newborn full-term infant in days following birth.
§ = Differentiation of Cells:
0 = Undifferentiated cells.
+ = Immature cells containing vesicular nucleus.
++ = Immature cells containing either a nucleolus or some cytoplasm.
+++ = Mature ganglion cells with prominent cell and nuclear membranes and abundant cytoplasm.

are undifferentiated with no visible cytoplasm and an irregular, nonvesiculated nucleus. At approximately 14 to 16 weeks there is a tendency toward elongated plexuses of cells which still are undifferentiated. By the time of 26 weeks' gestation (1,700 Gm. premature infant) this myenteric layer shows organization into definite plexuses which contain, in addition to the completely undifferentiated cells, some cells with vesicular nuclei. There are 3 to 4 plexuses per low-power microscopic field (1.55 mm. on tissue slide). Shortly after birth (full-term gestation), slightly more mature cells appear in the plexuses. These cells show more cytoplasm and occasional nucleoli. Mature ganglion cells

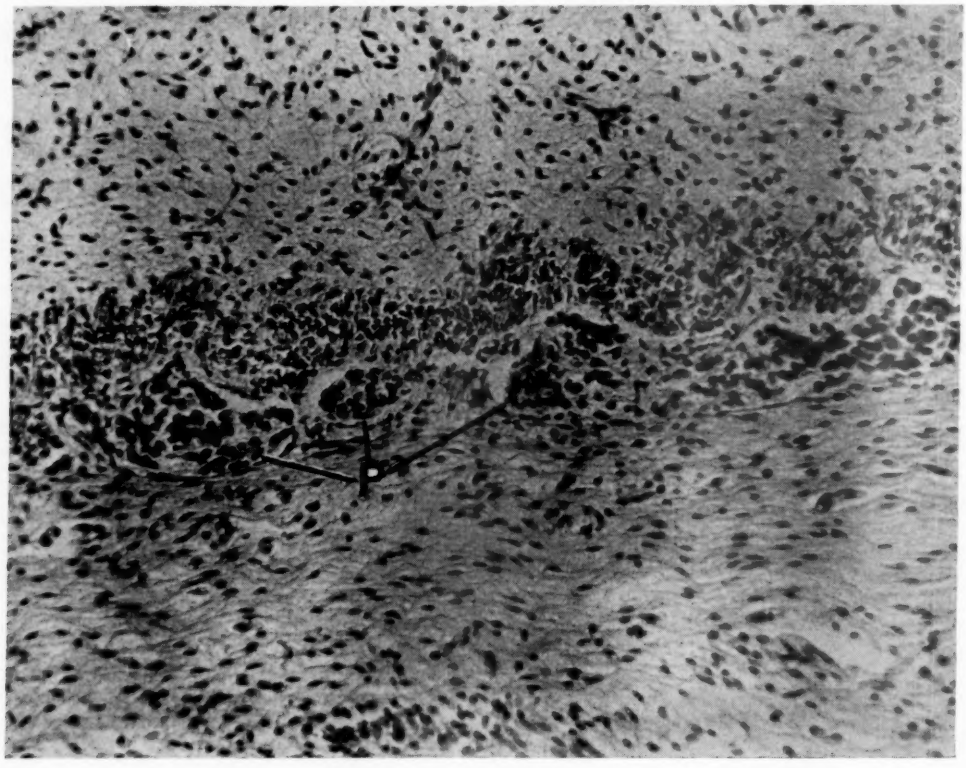

Fig. 1.—Photomicrograph of myenteric plexus layer in a pylorus of a 12-week fetus. Note the indistinct division of plexuses (*P*) into nests which contain large numbers of neurocytes. (×145.)

(abundant cytoplasm, prominent cell and nuclear membranes with nucleoli) first appear between the second and the fourth week after full-term gestation. This evidence of maturity is concomitant with a decrease in the number of undifferentiated cells in each plexus. The shift is toward differentiation so that recognizable mature ganglion cells regularly are present in the normal pylorus from 1 to 5 months and only a few undifferentiated cells are present (Fig. 2).

The stromal cells in the myenteric layer begin differentiation at about 26 weeks' gestation and mature at the same rate as stromal cells elsewhere in the pylorus.

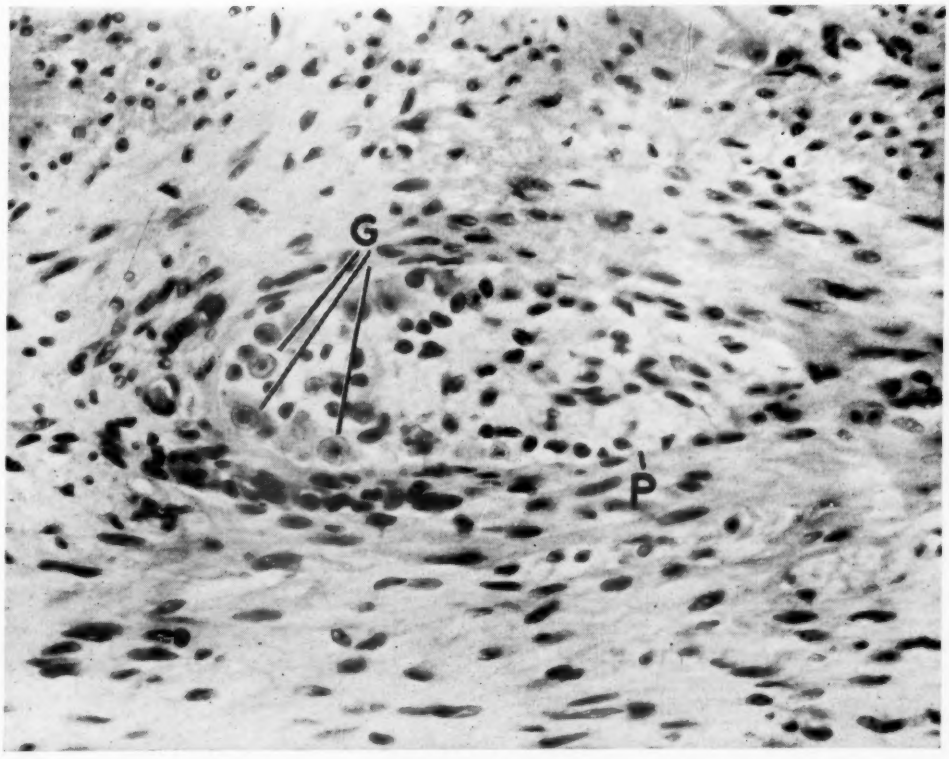

Fig. 2.—Photomicrograph of a normal Auerbach's plexus (*P*) in a pylorus containing mature ganglion cells (*G*) in a 30-day-old infant with normal pylorus. (×550.)

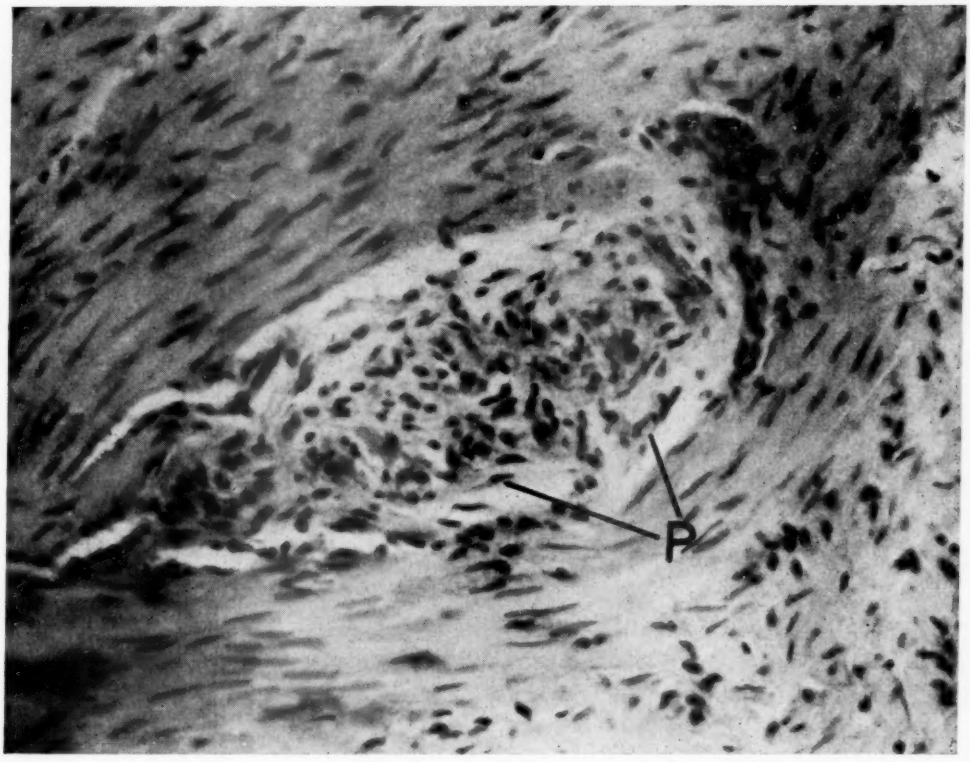

Fig. 3.—Photomicrograph of plexus (*P*) in a pylorus of a 42-day-old infant with hypertrophic pyloric stenosis. Note the absence of mature ganglion cells. (×550.)

The Pylorus of Infants With Hypertrophic Pyloric Stenosis (Table II).—The myenteric plexuses of the pylorus in infants with hypertrophic pyloric stenosis differ in appearance from that described as present in normal pyloruses (Fig. 3). The number of plexuses, or nests of cells, per unit area is essentially the same as the normal, but the number of mature ganglion cells is reduced so that most plexuses contain no such cells. A few plexuses contain one recognizable mature ganglion cell. On the other hand, all plexuses in the hypertrophic pylorus contain, as their predominant cell, many undifferentiated cells. Some cells show a degree of differentiation and a few demonstrate some cytoplasm with nucleoli. Generally the cells in the specimens of hypertrophic pyloric stenosis are more difficult to recognize as ganglion cells when contrasted with those of normal appearance.

TABLE II.—MYENTERIC PLEXUS OF THE PYLORUS IN INFANTS WITH HYPERTROPHIC PYLORIC STENOSIS

NO.	NAME	SEX	AGE IN WEEKS	NUMBER OF PLEXUSES PER LOW POWER FIELD (1.55 MM.)	NUMBER OF GANGLION CELLS PER PLEXUS ACCORDING TO DIFFERENTIATION†			
					0	+	++	+++
1.	R. B.	M	3½	1-3	21	12	0	0
2.	G. D.*	M	4	1-3	47	5	0	0
3.	B. S.	M	4	2	71	19	3	0
4.	B. F.	M	4	0-3	24	7	0	0
5.	C. C.	F	5	1-3	24	15	0	0
6.	S. C.	F	5	1-3	17	12	1	1
7.	J. R.	M	5	2-4	24	4	1	0
8.	D. T.	M	5	1-2	35	8	1	0
9.	P. W.	M	5	1-5	30	10	0	0
10.	B. NcN.	F	5	0-1	22	5	0	0
11.	D. V.	F	5	1-3	34	6	0	0
12.	D. C.	M	6	2-5	27	12	1	0
13.	D. W.	M	6	0-5	45	10	0	0
14.	M. L.	M	6	0-3	23	16	3	1
15.	C. S.	M	8	3-5	23	8	3	1
16.	R. P.	M	8	0-4	80	14	0	0
17.	C. J.	M	8	2-5	27	8	0	0
18.	S. M.	M	12	0-3	28	10	1	0
19.	B. B.	M	13	1-4	15	15	5	1

* = Autopsy specimen.
† = Differentiation of cells (as in Table I).

The usual appearance of the musculature of hypertrophic pyloric stenosis was present; the circular layer, much more prominent than the longitudinal layer, showed marked irregularity and disorganization of its muscle fibers.

DISCUSSION

The development of Auerbach's plexus in the normal pylorus of the human fetus and infant indicates that the nerve layer becomes segmented into plexuses at approximately 16 weeks' gestation, but the plexuses do not contain mature ganglion cells until two to four weeks after full-term birth. Normally by the time mature ganglion cells are evident in every plexus (4 to 8 weeks), the number of immature cells is reduced significantly. At this age, when most

infants with hypertrophic pyloric stenosis are operated upon (and biopsied, in this study), the plexus of the abnormal pylorus usually contains no mature ganglion cells. In addition, the plexus in hypertrophic pyloric stenosis contains many more undifferentiated and immature ganglion cells than are seen in normal pyloruses in infants of comparable age. It would appear from the tabulated data that the plexus of the hypertrophic pylorus has a cellular distribution similar to that seen in the normal pylorus several weeks earlier in age.

These cellular abnormalities, often described as degenerative, or disintegrated, may in reality be representative of plexuses and cells which have never completely developed. The observation that full maturity of ganglion cells is not apparent until well after birth tends to discredit any theory concerning degeneration of cells at that same period of time in hypertrophic pyloric stenosis. It appears more likely that final maturation of ganglion cells does not occur in hypertrophic pyloric stenosis.

There has been much speculation as to the significance of the ganglion cell changes in hypertrophic pyloric stenosis. The "degenerative" appearance of the ganglion cells has in the past been attributed to an ischemic effect of the contracted hypertrophic muscle, to infection, or to nerve cell exhaustion from unexplained vagotonia similar to that described by Ingersoll[7] with chronic vagal stimulation in rats. Nevertheless, from the studies reported here, it is believed that the abnormal histologic appearance of the plexus is significant and probably represents a failure of ganglion cell development. This developmental arrest, which could be of congenital etiology, might physiologically block the reflex control of the pylorus or at least cause a physiologic derangement of normal pyloric activity. Such a functional abnormality could cause repeated circular muscle spasm and work hypertrophy, as speculated by Halbertsma.[5]

It is conceivable also that the usual time of onset of symptoms in infants with hypertrophic pyloric stenosis is more than coincidental with the failure of the expected appearance of mature ganglion cells at that time. If the development of the plexus of the abnormal pylorus is arrested at a stage similar to that seen in the normal newborn infant, one could postulate that secondary muscle hypertrophy develops in the interval from birth to the onset of symptoms. In one instance in this study roentgenograms which were not abnormal were made on one infant (B.B., No. 19 in Table II) at 9 weeks of age; however, operation at the age of 13 weeks demonstrated hypertrophic pyloric stenosis. The plexus from this pylorus showed slightly more differentiation of cells than is usual in a case of hypertrophic pyloric stenosis.

That the changes are localized to the pylorus was well demonstrated in the study reported by Belding.[3] Failure of development of the ganglia also could exist as a local phenomenon when it is considered that the pylorus has its own nerve pathway of control[8] and that the pylorus of the experimental dog, isolated from the nerve and vascular supply of the rest of the stomach and duodenum, continues to function as a sphincter.[4]

Special attention is called to one set of monovular twins (C. C. and S. C., No. 5 and No. 6 in Table II) who were operated upon for hypertrophic pyloric stenosis. The first infant (C. C.) had pyloromyotomy with biopsy for frank

symptoms and signs of pyloric stenosis. No mature ganglion cells were seen in any plexus of the pylorus. The second child, who was operated upon 2 days later for "early" symptoms of hypertrophic pyloric stenosis, was found at operation to have only slight thickening of the pylorus. Nevertheless, a Ramstedt incision (with biopsy) was done. Microscopic study of this pylorus demonstrated the typical findings of hypertrophic pyloric stenosis: hypertrophy and disorganization of circular muscle fibers, decrease in the number of mature ganglion cells per plexus, and many immature ganglion cells. It is believed that the second identical twin was operated upon early in the clinical course before hypertrophy was fully developed grossly.

It is doubtful that the fewer than normal number of mature cells per plexus in the hypertrophic pylorus is accountable to disproportion in size of muscle mass, because of the finding that the number of plexuses per unit area is essentially the same in both the normal and the hypertrophic pylorus. Furthermore, as pointed out by Belding,[3] with muscle hypertrophy there is actual decrease in luminal size so that the perimeter at the level of the myenteric layer is not altered significantly.

Even though nonspecific methods for nerve staining were used in this study, the abnormalities in the number of ganglion cells per plexus and their histologic appearance were adequately discernible with the simpler staining preparations. The histologic appearance probably is significant when it is taken into consideration that fresh biopsy specimens were obtained surgically for study from living infants with hypertrophic pyloric stenosis.

SUMMARY AND CONCLUSIONS

From a histologic study of the myenteric plexus layer of the pylorus of the human fetus, the normal infant, and the infant with hypertrophic pyloric stenosis, certain observations have been made. The layer, continuous at first, becomes segmented into plexuses or nests of cells. The number of plexuses per unit area in the normal and abnormal pylorus of the infant are essentially the same. Normally the ganglion cells progress to maturity so that mature forms appear shortly after full-term birth and immature cells decrease in number. In hypertrophic pyloric stenosis mature ganglion cells rarely are present and many undifferentiated and immature cells dominate the plexus.

Pyloric tissue was obtained by surgical biopsy from 19 patients with hypertrophic pyloric stenosis, and compared with autopsy specimens of pyloruses from fetuses and infants.

The significance of the histologic abnormality of the ganglion cells is not known. It appears that failure of development or maturation of the ganglion cells is present, rather than degeneration of them, in hypertrophic pyloric stenosis. These findings probably portend an abnormal pyloric function.

This study, started at the instigation of Dr. Herbert C. Miller, Chairman of the department of Pediatrics, University of Kansas Medical Center, has been carried out with the generous assistance and cooperation of the staff of the Pediatrics Department.

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ENDOCRINE CONTROL OF MAMMARY GLANDS IN C_3H MICE

DONALD J. FERGUSON, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota and the Laboratory of Experimental Surgery, Veterans Administration Hospital)

ENDOCRINE factors involved in the normal development and maintenance of the mammary glands have been extensively studied, but are not fully understood, especially as they apply in any particular strain of mice. It seems probable that hormones controlling the normal mammary gland are similar to, or perhaps identical with, those required for mammary carcinogenesis. Intensive study of endocrine control of noncancerous mammary tissue in C_3H mice may accordingly help to specify more clearly the hormonal background required for carcinogenesis in this high mammary cancer strain. The present study aims to describe, in terms of pituitary and other hormone preparations at present available, the requirements for normal mammary gland maintenance (excluding changes associated with pregnancy) in C_3H female mice after removal of the pituitary, gonads, and, in a few animals, also the adrenals.

METHODS

Female mice of the C_3H strain were hypophysectomized (H), hypophysectomized and castrated (H-C), or hypophysectomized, castrated, and adrenalectomized (H-C-A) at 3 to 5 months of age. One adrenal was removed with the other organs, and the remaining adrenal was removed on the day injections started. The difficulty in maintaining H-C-A mice resulted in survival of only 10 per cent (7 mice) of those prepared. Many sections of suspected areas failed to reveal residual adrenal tissue in these seven animals.

Body weights were obtained weekly. Completeness of hypophysectomy was determined primarily by observation of body weight changes, and was confirmed by serial sections of the decalcified sella turcica in 18 animals. Vaginal smears were obtained by lavage. Controls were the same age as the experimental animals.

Water and Purina fox chow were given ad libitum. Saline solution (0.45 per cent) and glucose (2.5 per cent) were given in drinking water after adrenalectomy. Mice were singly housed in a constant temperature room.

Pituitary hormones, thyroxin, and cortisone in saline solution or suspension were injected subcutaneously into the dorsal midline daily or twice daily. The total daily volume injected was 0.1 ml. Other steroids were given in oil injections once daily in a total volume of 0.03 ml. per day. Hormones and doses are listed in Table I. Injections were begun thirty to thirty-eight days after operation and continued for fourteen days unless otherwise stated. On the day after the last injections, the animals were killed with ether, mammary whole mounts were prepared, and tissue sections were made.

RESULTS

Mammary Glands in Intact Mice.—A study of 42 whole mount biopsies taken from 28 virgin female mice, aged 3 to 7 months, at various stages of the estrous cycle, failed to show any consistent cyclic change or any difference between animals when several glands were examined from each.

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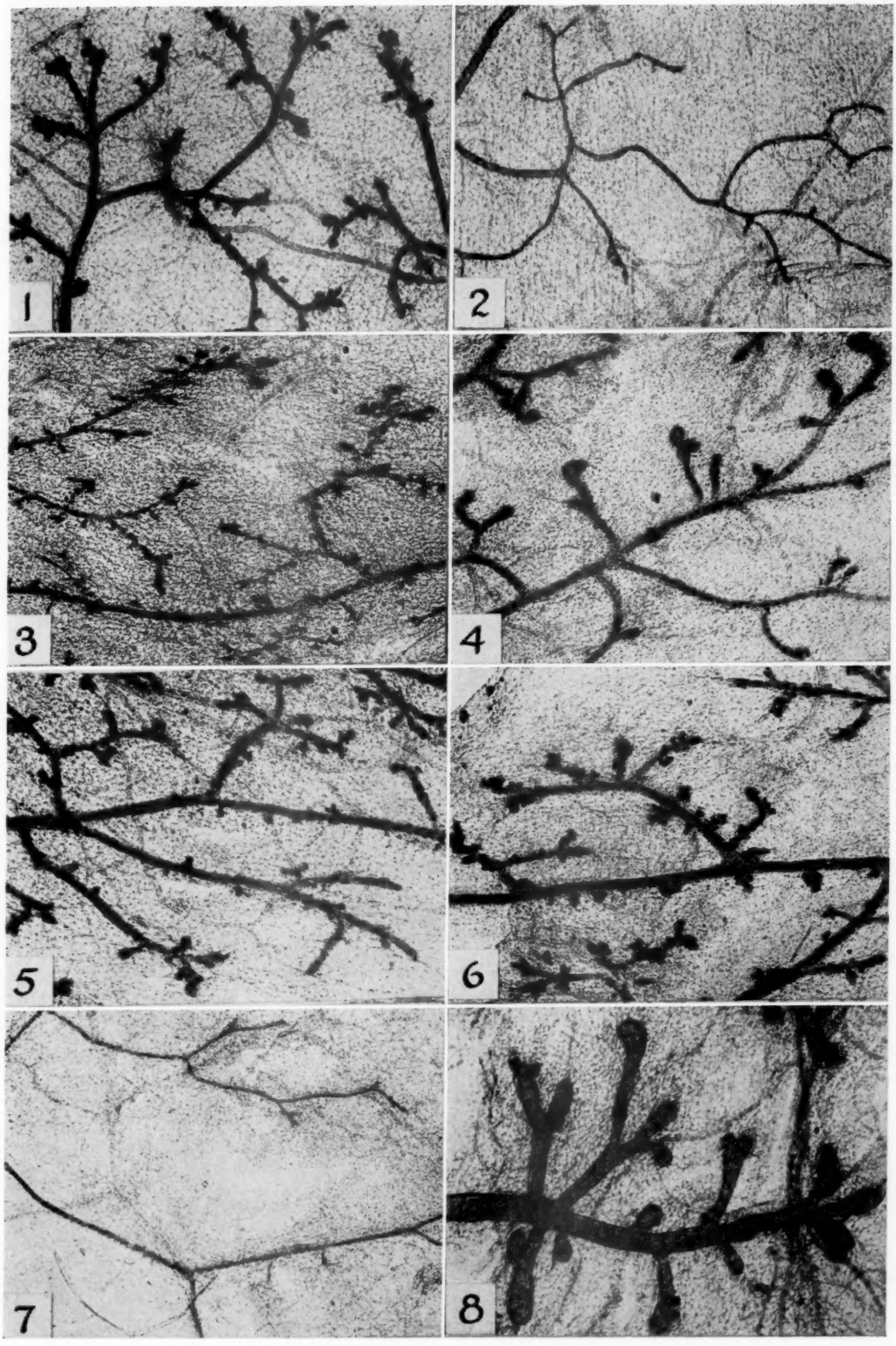

Fig. 1.—Photomicrographs of mammary gland whole mounts from female mice. (Hematoxylin and eosin, ×30; reduced ⅙.) *1*, Intact control; *2*, H-C, no hormone, 6 weeks after operation; *3*, H-C, estradiol and prolactin. Glands of H-C-A mice given these hormones had the same appearance; *4*, H-C, estradiol and growth hormone; *5*, H-C, estradiol, progesterone, and growth hormone; *6*, H-C, estradiol, progesterone, growth hormone, and prolactin. Although slightly different from *1* this gland would not be distinguishable in a group of intact controls; 7, H-C 257 days after operation, given stilbestrol daily 227 days; *8*, Castrated sham-hypophysectomized, underfed control for mouse in 7 died after 195 days of stilbestrol injections.

TABLE I. HORMONE PREPARATIONS USED, DAILY DOSES, AND CRITERIA FOR APPROXIMATION OF MINIMUM DOSE GIVING MAXIMUM EFFECT IN HYPOPHYSECTOMIZED-CASTRATED MICE
(From 9 to 20 mice were tested with each hormone, using 3 or 4 dose levels, except where otherwise noted)

PREPARATION	DOSE	CRITERIA FOR EFFECTIVE DOSE
Alpha-estradiol	0.01 μg	Uterine weight gain, 14 days
Cortisone acetate	50 μg*	Arbitrary; 1 μg eosinopenic†
Diethylstilbestrol	0.08 μg	Uterine weight gain, 14 days
Progesterone	0.02 mg.	Inhibition of estrogen effect on vagina, 5 days
Testosterone propionate	20 μg	Seminal vesicle weight gain, 14 days
Thyroxin	0.5 μg	Body weight gain, 28 days
Adrenocorticotropin (Acthar, Armour)	1.0 mg.*	Arbitrary; 0.5 mg. more eosinopenic than saline
Gonadotropin, hog pituitary (Armour)	0.5 mg.	Vaginal cornification hypophysectomized mice, 3 days
Gonadotropin, pregnant mare serum (Upjohn)	3.0 i.u.	Vaginal cornification hypophysectomized mice, 3 days
Growth hormone (Armour, G.H.3)	20 μg	Body weight gain, 7 days
Prolactin (luteotrophin, Squibb)	20-25 i.u.*	Arbitrary; effect shown, Table II

*Divided into 2 doses daily.
†Speirs and Meyer, 1949.

Morphology After Removal of Endocrine Glands.—There is no difference in the appearance of mammary glands from hypophysectomized female mice and from mice in which the ovaries or ovaries and adrenals have also been removed. Atrophy proceeds at a diminishing rate for at least six months, but is quite pronounced after one month. At that time the main ducts are slender, there are few branches, and no alveoli or end buds (Fig. 1, *2* and *7;* Table II).

TABLE II.—HORMONE COMBINATIONS WHICH AFFECTED MAMMARY GLANDS IN HYPOPHYSECTOMIZED FEMALE MICE

HORMONES*	NUMBER OF MICE	DIAMETER OF TERMINAL DUCTS† (μ)	NUMBER OF END BUDS‡	NUMBER OF ALVEOLI§	AVERAGE DIAMETER OF OVARIES (MM.)
None (control)	4	10-20	0	0	0.7
Prolactin‖	3	10-20	0-2	0-4	0.9
Prolactin (local)‖	3	25-70	0-5	0-24	
Prolactin—estradiol	3	20-40	38-45	0-3	0.8
Prolactin (local)—estradiol	3	20-70	23-54	0.5	
Pituitary gonadotropin	4	10-35	0-5	0-9	0.9
Pregnant mare serum gonadotropin	4	10-25	0-4	0-8	1.1
Pituitary gonadotropin—prolactin	3	15-25	2-3	2-31	1.8
Pregnant mare serum gonadotropin—prolactin	4	15-25	0-2	3-39	1.8

*Full names and doses in Table I.
†Range. Terminal ducts 0.5 to 1.0 mm. long, including short branches.
‡Range on single glands of second or third pair.
§Range on terminal ducts.
‖In 2 H-C females, the results were similar.

Steroid Hormones, Stilbestrol, and Thyroxin.—Given in the doses indicated in Table I, these hormones did not affect morphology of the mammary gland in H-C mice when given singly, or in the following combinations: estradiol-progesterone, estradiol-testosterone, and stilbestrol-testosterone. From 4 to 10 mice were used for each test. (Some of these data were previously reported by Ferguson and Visscher.[2])

The effects of prolonged administration of 0.1 mg. daily of stilbestrol, given subcutaneously in alcohol-aqueous solution, were studied in 9 female H-C and 7 castrated and sham-hypophysectomized underfed controls maintained at the same body weight as the H-C mice, which survived 165 to 315 days after operation. Continuous subestrous vaginal smears were found in all mice. The mammary glands in H-C mice were unaffected, but controls had widened ducts without alveoli (Fig. 1, *7* and *8*). The average weight of uterine horns in the H-C mice was 22.4 mg., and in the controls, 27.3 mg. In 12 untreated H-C mice the uterine horns weighed 2.7 mg. These data show that the dose of estrogen given was effective in maintaining uterine weight and vaginal cornification, though it had no effect on mammary glands.

Most of these mice at the time of death were beyond the average cancer age of intact controls, which is thirteen months. Total mammary cancer incidence in virgin female is over 65 per cent in the same colony. There were no hyperplastic nodules in the hypophysectomized mice, but a few were found in the controls.

Pituitary Hormones.—

Gonadotropins: There were 3 or 4 mice in each subgroup of this experiment. In H-C females, gonadotropins without estrogen had no effect on the mammary glands, but in H females, gonadotropins alone produced a considerable increase of branching and end buds with occasional alveoli. In H mice receiving pregnant mare serum gonadotropin, vaginal smears showed abundant cornified cells after the third day, and ovaries were moderately enlarged with many follicles and a few corpora lutea (Table II). Pituitary gonadotropin had a similar effect but to a lesser degree. Estrogen did not augment the effects of PMS gonadotropin in H mice, but prolactin plus PMS gonadotropin greatly increased alveolar and duct growth, and ovaries were enlarged with follicles and corpora lutea (Table II). Vaginal smears in these mice showed inhibition of cornification as compared with the effect of PMS gonadotropin alone. These data illustrate a luteotrophic effect of this prolactin, and a synergistic effect of prolactin with gonadotropin on the ovaries, and they suggest the need for removing adrenals, which might secrete progesterone in response to prolactin, in a control group. Adrenal histology and size did not vary among any of the subgroups just described, however.

Prolactin: When injected just beneath the second nipple in 3 H and in 2 H-C female mice, prolactin produced a local effect, as was originally shown in the rabbit by Lyons.[6] The injected glands showed widened ducts with dense proliferation of cells immediately surrounding the ducts, and development of end buds and a few alveoli. Glands on the other side of the same animals were affected slightly or not at all. When estradiol was given additionally in a

neutral location, mammary development occurred bilaterally (Fig. 1, *3;* Table II) but was much increased at the site of local injection of prolactin. The local injection of estradiol, with or without prolactin, was without special local effect. These experiments show that a high concentration of prolactin can affect the mammary gland in the absence of the pituitary, gonads, and exogenous steroids, and confirm the fact that prolactin acts directly on the mammary tissue.

Estradiol plus prolactin affected the mammary glands in 5 H-C-A mice just as it did those in H-C mice, which indicates that adrenal steroids did not play a role in the action of prolactin on the mammary gland in H-C mice. Microscopic evidence of lactation was not seen in any mammary glands in the present study.

Other Pituitary Hormones Given Separately: From 3 to 10 mice were used in each subgroup. No detectable effect on mammary glands in H-C mice was observed after injections of growth hormone, ACTH, or either gonadotropin. Thyrotropin was not studied. Gardner and White[4] found it inactive on mammary glands of hypophysectomized male mice when given with estrogen. Thyroxin was without effect on mammary glands, but augmented the effect of growth hormone on body weight. Growth hormone alone or in combination increased body weight to the preoperative level or higher in every mouse.

Combinations of Pituitary and Steroid Hormones.—

Growth hormone plus estradiol or stilbestrol: When given to H-C females this combination produced a characteristic overdevelopment of end buds and widening of ducts (Fig. 1, *4* and Table III), no alveoli being formed. The addition of thyroxin or of ACTH to this combination had no apparent effect. Continuation of the injections for thirty days in 4 animals produced little further change.

TABLE III. HORMONE COMBINATIONS AFFECTING MAMMARY DEVELOPMENT IN HYPOPHYSECTOMIZED-CASTRATED AND HYPOPHYSECTOMIZED-CASTRATED-ADRENALECTOMIZED‖ FEMALE C_3H MICE

HORMONES*	NUMBER OF MICE	DIAMETER OF TERMINAL DUCTS*	NUMBER OF END BUDS*	NUMBER OF ALVEOLI*
None (intact control)	28	15-70μ	0-11	5-84
None (H-C and H-C-A)	14	10-20	0	0
Growth hormone, estrogen†	19	15-50	6-30	0
Growth hormone, estradiol, progesterone‡	5	20-50	28-86	0-6
Growth hormone, estradiol, prolactin§	8	15-40	15-63	0-26
Growth hormone, estradiol, progesterone, prolactin§	8	20-50	2-4	3-33
Estradiol, prolactin‖	13	15-30	10-24	0-9
Estradiol, progesterone, prolactin	3	20-30	3-9	3-34

*Same as Table II.

†Also received thyroxin, 8 mice; ACTH, 4 mice.

‡Also received thyroxin, 3 mice.

§Also received thyroxin, 4 mice.

‖Five mice receiving estradiol-prolactin H-C-A; all others in this table H-C except 2 controls H-C-A and the 28 intact mice.

Growth hormone, estrogen, and progesterone in H-C mice produced a larger number of smaller end buds, and a few alveoli (Fig. 1, *5*); when prolactin

was given in place of progesterone, the effect was similar, but there were more alveoli and fewer end buds.

Growth hormone, estrogen, progesterone, and prolactin: This combination produced a gland closely resembling the normal (Fig. 1, *6*).

Prolactin, estradiol, and progesterone: These produced a nearly normal morphology, but the structures were small and not fully grown as when growth hormone was given.

The combination of ACTH and estrogen had no effect. Either gonadotropin plus estrogen produced a slight growth of ducts and end buds. Four animals were used in each of these three groups.

DISCUSSION

The present experiments are preliminary to further study of the hormonal influence affecting mammary carcinogenesis in C_3H mice. The available data on endocrinology of the mammary gland do not necessarily apply to this particular species and strain, and effective dose levels of injected hormones also may vary according to sex, age, and presence or absence of pituitary and gonads. Doses in the present experiment are not, of course, necessarily optimum, but they have been shown to be in the effective range.

In the hypophysectomized and castrated rat, estrogen, progesterone, and prolactin have been found necessary for lobule and alveolar mammary growth and prolactin was more effective when growth hormone and ACTH were present as impurities (Nelson).[7] Except for ACTH, the combination effective in H-C C_3H mice is the same.

The effects of unwanted fractions in pituitary hormones used in these experiments can be partly evaluated. Thus prolactin, which contains ACTH, growth hormone, gonadotropin, and thyrotropin in small quantities, has actions which the other factors, separately or in certain combinations, and in higher concentration, do not have. The effectiveness of gonadotropin alone on mammary growth in H mice could be explained by the presence in gonadotropin of prolactin-like material acting with ovarian steroids. The relative failure of gonadotropin plus estrogen in H-C mice may indicate that the amount of prolactin-like substance is inadequate in the absence of progesterone.

It is probable that hormones must stimulate and maintain a certain minimum growth of mammary tissue before mammary cancer can arise. The strain-limited tendency to develop mammary tumors in mice may be further associated with differences in the hormonal environment, or in susceptibility to hormones, which are under genetic control (Bittner and associates[1]; Heston and Andervont[5]). Although attention has been mainly focused on estrogen, differences in the incidence of mammary cancer in mice of various strains have not been associated with measurable differences in the amounts of estrogen produced by the animals (Gardner[3]). In C_3H mice it is evident that pituitary hormones are as essential as estrogen for mammary development and probably for mammary cancer; prolactin, in fact, is effective in the virtual absence of steroids, whereas estrogen is not effective in the absence of pituitary hormones.

SUMMARY

Beginning one month after removal of pituitary, gonads, and in some cases, also the adrenals, C_3H female mice were injected daily for fourteen days with various combinations of hormones, the doses of which were shown to be in an effective range, and the effects on the mammary glands were studied.

Restoration of the atrophied glands to a normal appearance was obtained with a combination of estradiol, progesterone, prolactin, and growth hormone in hypophysectomized-castrated females. The effect of estradiol plus prolactin was the same in hypophysectomized-castrated and hypophysectomized-castrated-adrenalectomized female animals. Prolactin alone stimulated mammary growth locally when injected in the region of a gland in the absence of pituitary and gonads.

In hypophysectomized-castrated mice, daily administration of stilbestrol for up to 315 days after operation had no effect on mammary glands, though the uterus and vagina were strongly affected.

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THE PRODUCTION AND EVALUATION OF ASCITES SECONDARY TO ISOLATED TRICUSPID INSUFFICIENCY IN DOGS

MITCHELL W. SPELLMAN, M.D., PH.D.,* AND BASDEO BALKISSOON,** M.D.,
WASHINGTON, D. C.

(From the Departments of Surgery an Physiology, Howard University School of Medicine)

IN EARLIER experimental studies a sustained and severe ascites resolved following total adrenalectomy in two dogs with large, chronic, bilateral arteriovenous fistulas in the hind extremities.[1] This observation occurred concomitantly with similar reports on the effects of adrenalectomy from the laboratories of Davis[2] and Hamilton.[3]

The results of a related investigation suggested that the influences of total adrenalectomy upon cardiac output in dogs with arteriovenous fistulas were determined primarily by the character of the maintenance therapy.[4] Thus, dogs with large left-to-right shunts, appropriately maintained on a regimen of cortisone and supplementary sodium chloride, sustained a cardiac index of even greater magnitude than that observed in the comparable animals with intact adrenals. Total adrenalectomy in similar animals, except that adequate replacement was accomplished with DOCA alone, resulted in a significant diminution in the cardiac index. Upon the basis of these data, we have questioned whether the effects on ascites mediated by adrenalectomy are explicable solely upon alterations in the renal excretion of soduim and water.

This report describes an effort to provide an experimental animal with sustained ascites secondary to a reproducible cardiac lesion. The production of experimental ascites by isolated tricuspid insufficiency, in contrast to other methods, is not only independent of vena caval constriction but, moreover, the lesion resides in a single valve rather than in combined defects involving multiple valves. This approach suggests a basis for establishing a more direct relationship between ascites and cardiac function which is of experimental value, since the status of both may be crucially influenced by adrenalectomy.

Tricuspid insufficiency is reported to produce significant elevation of venous pressure without myocardial failure and, additionally, to effect physiologic responses which are somewhat similar to those of an arteriovenous fistula.[17, 19] Indeed, it is surprising that neither ascites nor chronic congestive heart failure appears to have occurred previously in experimental animals with isolated tricuspid insufficiency.

METHODS

Experimental Animals.—Healthy mongrel dogs of both sexes, the weights of which varied from 15 to 25 kg., were utilized for the study. The diet consisted of kibbled biscuits and

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*John and Mary R. Markle Scholar in Medical Sciences and Assistant Professor of Surgery.

**Resident in Surgery, Freedmen's Hospital, Washington, D. C., and Research Assistant, Departments of Surgery and Physiology, Howard University School of Medicine.

dog ration supplemented daily with one-half pound of horse meat. Neither the diet nor the mineral intake was manipulated and the average daily ingestion of sodium remained approximately 1 gram.

Production of Ascites.—Ascites was secondary to the production of severe tricuspid insufficiency by the division of the chordae tendineae of the tricuspid valve. After a preoperative hypodermic injection of morphine sulfate (4 mg. per kilogram body weight), the dogs were anesthetized with intravenous sodium pentobarbital (15 mg. per kilogram body weight) and positive pressure maintained through an endotracheal tube. The animals were operated upon through a right thoracotomy at the level of the fifth intercostal space. Initially, a variable number of the chordae tendineae of the tricuspid valve were severed, after the method of Sprafka, Haddy, Alden, and Baronofsky,[5] utilizing a small right ventriculotomy through which a snare engaged the chordae. The technique as applied here could not be designed to create standardized or reproducible lesions so that it was necessary to evolve another approach.

All of the animals with tricuspid insufficiency which underwent definitive study had division of the chordae tendineae performed through a large right atrial incision while employing total temporary inflow occlusion of the venae cavae and the azygous vein. The duration of the venous occlusion varied from one and one-half to two and one-half minutes. The chordae tendineae supporting each cusp were systematically isolated and individually severed in an effort to achieve partial or total loss of function of the tricuspid valve (Fig. 1). Massive regurgitation into the right atrium or "ventriculization of the atrium"[15] which results from total defunctionalization of the tricuspid valve was the ultimate goal of the operative procedure.

The familiar mechanism for effecting venous inflow stasis with the aid of umbilical tapes which constrict the superior and inferior venae cavae is demonstrated in Fig. 1. Concomitantly, the azygous vein was temporarily occluded with a ligature. A generous atriotomy was employed which assured adequate exposure and visualization of the tricuspid valve. After the chordae tendineae had been divided, the margins of the atrial incision were approximated with the aid of a Satinsky or a Harkins atrial clamp and the venous inflow re-established by releasing the occluding tapes. With the use of this maneuver, a secure and unhurried closure of the atriotomy wound was accomplished with a continuous suture of 4-0 silk (Fig. 1). When the atrial clamp was removed, the marked distention of the pulsating right atrium and the pronounced thrill were impressively demonstrable. With each ventricular systole, obvious tricuspid regurgitation propagated a fluid wave which was transmitted from the atrium into both venae cavae for a distance of several centimeters. The regurgitant volume was visibly augmented when azygous flow was reconstituted; for this reason its ligation was avoided. We have designated as "severe" tricuspid insufficiency this example of total or nearly complete tricuspid incompetence. In conclusion, the pericardial incision was approximated throughout its length with interrupted silk sutures as a measure to restrain the enormous atrial distention.

Evaluation of Ascites and Ascitic Fluid Production.—The magnitude and gross variations in the ascites were assayed by a careful daily measurement of the body weight. Thorough abdominal paracentesis was performed approximately each two weeks so that ascitic fluid production was calculated quantitatively utilizing this time interval as a standard of reference.

Hepatocellular function was estimated as a relationship of the plasma retention of rose bengal dye, as initially suggested by Delprat,[6] and the bromsulphalein test[7] performed as a measure to evaluate the significance of the results with the former method.

Measurement of Peripheral Venous Pressure in Ascites.—The jugular and femoral vein pressures were recorded at intervals of two to four days following the creation of tricuspid incompetence, and even more frequently as the onset of ascites was anticipated. To avoid the frequent errors and variations encountered in measuring peripheral venous pressure, a standardized technique which provided a constant base of reference was meticulously employed. We adopted the familiar apparatus described by Moritz and von Tabora[8a]

whose method and instrument were more recently modified by Lyons and his associates.[8b] Manometer tubing of 7 mm. bore and a needle of gauge 18 were utilized. The venous pressures were always measured in the supine position with the reference point 80 mm. anterior to the skin of the back.

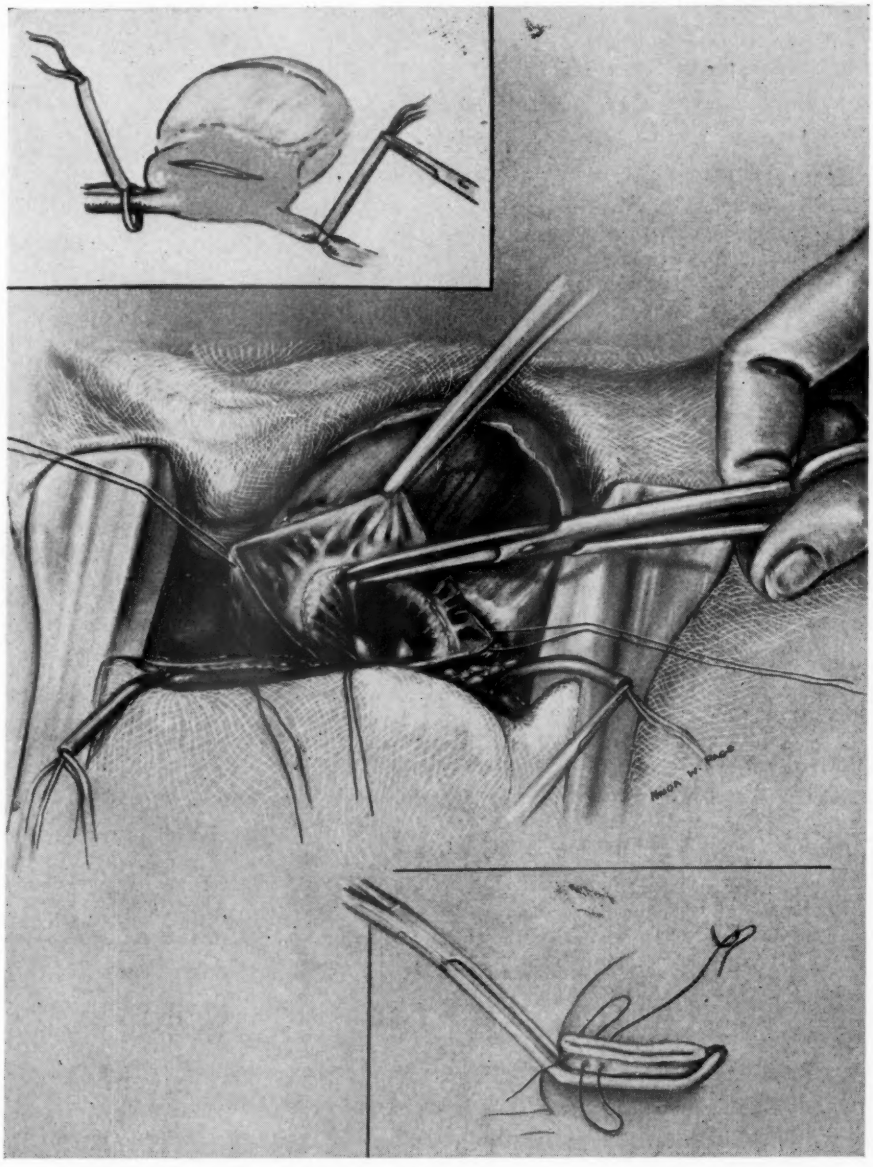

Fig. 1.—Creation of tricuspid insufficiency. Operative approach for division of chordae tendineae of tricuspid valve under direct vision.

Necropsy Examination and Organ Weights.—Each experimental animal which succumbed underwent a detailed post-mortem examination. The heart, liver, spleen, kidneys, and adrenals were carefully inspected and weighed, and specimens retained for histologic study. The heart was most critically surveyed, and the integrity of the tricuspid valve and its chordae tendineae were evaluated and recorded.

More detailed physiologic studies which included measurements of the plasma and extracellular fluid volumes, total body water, radiosodium space, hepatic function, plasma and ascitic fluid protein, and other parameters are described elsewhere.[9]

TABLE I. RELATIONSHIPS BETWEEN THE SEVERITY OF ISOLATED TRICUSPID INSUFFICIENCY AND EXPERIMENTAL ASCITES IN DOGS

DOG NO.	NUMBER OF TRICUSPID VALVE CUSPS DEFUNCTIONALIZED; AS ESTIMATED AT OPERATION	EVALUATION OF THE INTEGRITY OF THE TRICUSPID VALVE AT POST-MORTEM EXAMINATION	EXPERIMENTAL RESULTS	
			DEVELOPMENT OF ASCITES	COMMENTS
6†	All chordae tendineae of 2 cusps divided; chordae of septal cusp intact	Same as estimated at operation	No ascites demonstrable after 21 days postoperatively	
7†	All chordae of 2 cusps divided; chordae of septal cusp intact	Chordae of septal and anterior cusps intact; all chordae of posterior cusp divided	No ascites demonstrable after 26 days postoperatively	
8*	All chordae of 2 cusps divided; chordae of septal cusp intact	Same	Ascites demonstrable after 25 days postoperatively; relented after 98 days	Autopsy: Severe hepatic congestion
9†	All chordae of posterior cusps divided; chordae of septal and anterior cusps intact	Same	No ascites demonstrable 20 days postoperatively	
10*	All chordae of 2 cusps divided; septal cusp intact	Same	Mild ascites (1,380 c.c.), Pleural effusion (1,000 c.c.), and pulmonary edema at necropsy	No ascites demonstrable prior to death, 52 days after direct-vision operation
11†	Chordae of posterior cusp divided; remaining cusps intact	Some chordae of both anterior and posterior cusps divided; part of these and chordae of entire septal cusp intact	No ascites demonstrable after 27 days postoperatively	
12	All chordae of entire tricuspid valve divided	Animal still survives	Ascites demonstrable 25 days postoperatively	Progressively severe ascites now of 7 months' duration
13†	All chordae of 2 cusps divided; septal cusp intact	Survives	No ascites demonstrable 89 days postoperatively	
14	All chordae of entire tricuspid valve divided	Same	Severe, unrelenting ascites after 17 days postoperatively	Ascites, pleural effusion, pulmonary edema at death 40 days postoperatively
15†	All chordae of entire tricuspid valve divided	All chordae divided except two chords to the septal cusp and one chord to the anterior cusp	No ascites 84 days postoperatively	Severe hepatic congestion demonstrable 84 days postoperatively by liver biopsy
19	All chordae of entire tricuspid valve divided	Survives	Ascites demonstrable 14 days postoperatively	Ascites relented; completely resolved after 3d postoperative week
20	All chordae of entire tricuspid valve divided	Same	Ascites demonstrable 13 days postoperatively	Severe, progressive ascites with death 16 days postoperatively. Autopsy: Ascites, pleural effusion, hepatic congestion, and pulmonary edema

*Underwent previous operation employing right ventriculotomy, with or without venous inflow occlusion. Several chordae were divided but no significant tricuspid insufficiency ensued and both dogs were reoperated upon utilizing inflow occlusion, right atriotomy, and division of chordae tendineae under direct vision.

†After the interval of observation indicated, these dogs were utilized for another experimental study.[11, 20]

RESULTS

With the technique of Sprafka and associates,[5] which employs a small right ventriculotomy, the most serious difficulties encountered were inadequate exposure and visualization so that we were unable to produce anatomic defects which conformed in location and magnitude. Utilizing a larger right ventriculotomy with concomitant venous inflow occlusion assured adequate exposure but the requisite duration of inflow stasis was not tolerated. Two of the animals in which severe tricuspid incompetence was produced by this method of Robicsek and associates[10] did not survive intervals of inflow occlusion which approximated four minutes. When the caval constriction was released, the right atrium became massively dilated and ventricular fibrillation ensued. Efforts at resuscitation were futile.

In contrast, excellent exposure, precise availability of each individual chord for division under inspection, avoidance of direct injury to the valve cusp, and a mechanism for rapid and effective closure of the cardiotomy within the limits of cardiac tolerance were provided by the direct-vision technique utilizing right atriotomy (Fig. 1). The entire tricuspid valve could be defunctionalized through the atriotomy and the margins of the atrial incision securely approximated with an appropriate clamp within periods of inflow occlusion which varied from one to three minutes. Inflow stasis of this duration was remarkably well tolerated despite the severity of the resultant tricuspid regurgitation. Utilizing this technique there was an operative mortality of only 15 per cent, and during one interval twelve animals underwent this procedure without an operative fatality.

It beame apparent that neither grossly detectable tricuspid regurgitation nor an elevated right atrial pressure occurred with the division of the chordae tendineae of one cusp of this valve, regardless of its location. However, the mean right atrial pressure, when measured in four dogs at operation immediately following severance of the chordae tendineae of the entire tricuspid valve, varied from 108 to 120 mm. of saline. Division of the chordae tendineae which support two cusps of the tricuspid valve, as well as total defunctionalization of the whole valve, was usually well tolerated and was never a primary factor in the failure of a previously normal dog to survive the operative procedure, except where the effects of prolonged inflow stasis and anoxia appeared to contribute preponderantly. When venous occlusion times were retained within the limit of three minutes and the usual precautions to avoid hemorrhage were observed, no operative mortality occurred.

The tolerance to increasing tricuspid incompetence is well displayed by Dog 8. Initially, an operative procedure utilizing ventriculotomy[5] was performed and a snare employed to engage and sever four chordae. When ascites failed to develop after 58 days of observation, reoperation was undertaken under direct vision combining inflow occlusion with right atriotomy. At this time there was a palpable thrill overlying the right atrium, and inspection, with the aid of cardiotomy, revealed that most of the chordae tendineae of the posterior cusp had been divided during the previous operation. At this juncture, the remaining chordae of the posterior cusp and all chordae attached

to the anterior cusp were severed. Ascites was demonstrable on the twenty-fifth postoperative day, although subsequently it relented (Table I).

The experimental observations below are largely confined to animals in which the entire tricuspid valve or most of it was deprived of the support of its chordae tendineae.

Evaluation of the Severity of the Experimental Ascites.—Body weight: The body weight of this group of animals was increased from a mean control value of 18.2 ± 3.0 kg. to a mean value with ascites of 19.3 ± 3.7 kg. The resultant average increment in body weight of 1.1 kg. in the ascitic dogs is not statistically significant. The total body weight as a reflection of the severity of ascites is a relatively insensitive indicator since the magnitude of the losses in tissue mass is obscured by the weight of the ascitic fluid, except for the body weights which are measured immediately following paracentesis. Despite the limitations of the method, periodic paracenteses effectually demonstrated striking fluctuations in the body weight of a dog with tricuspid insufficiency and sustained ascites (Fig. 2). The unusual absence of substantial tissue

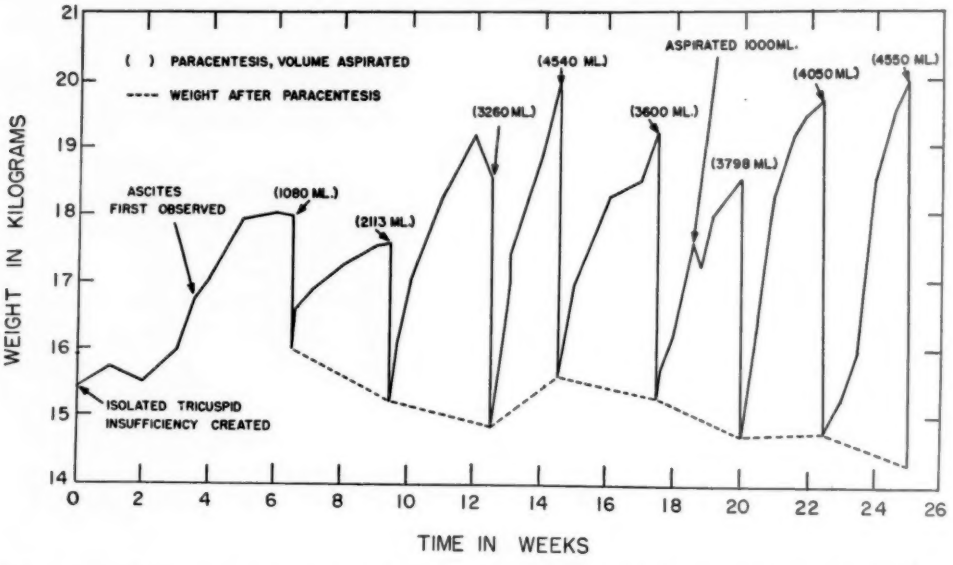

Fig. 2.—Periodic paracentesis and body weight alterations in an ascitic dog with isolated tricuspid insufficiency (Dog 12).

weight loss in this animal parallels its great tolerance for the severe ascites. The maximal augmentation of body weight as the consequence of ascites was often attained within three weeks following the production of severe tricuspid incompetence. However, this maximum ascitic weight level as a proportion of the mean control body weight had no constant correlation with the ultimate severity or fate of the ascites nor with the duration of survival (Tables I and II). The chronic progression of the unrelenting ascites in Dog 12 was unique in that the maximal weight attained with ascites, 29 per cent greater than the control value, was not realized until more than 100 days after the production of isolated tricuspid insufficiency (Table II and Fig. 2). There were variations between this extreme and the postoperative courses observed in Dog 19 and Dog 20 (Table II).

TABLE II. ASCITES IN DOGS WITH ISOLATED TRICUSPID INSUFFICIENCY: MAXIMUM BODY WEIGHT ATTAINED AND DURATION OF THE POSTOPERATIVE INTERVAL FOLLOWING PRODUCTION OF TRICUSPID INSUFFICIENCY

DOG NO.	MEAN CONTROL WEIGHT (KILOGRAM)	MAXIMUM WEIGHT WITH ASCITES (KILOGRAM)	PROPORTIONAL INCREASE (PER CENT) REPRESENTED BY ASCITIC WEIGHT / CONTROL WEIGHT × 100	DURATION OF POSTOPERATIVE INTERVAL (DAYS)	
				BEFORE APPEARANCE OF ASCITES*	BEFORE MAXIMAL WEIGHT ATTAINED
8	15.3	19.2	26.1	25	42†
12	15.4	19.9	29.0	25	101
14	15.6	18.2	16.6	17	21
19	15.6	16.5	6.0	14	17†
20	21.1	23.0	9.0	13	16

*Mean duration of postoperative interval before appearance of ascites was 19 days.
†Ascites spontaneously relented thereafter.

Volume of ascitic fluid production: Periodic paracentesis and measurement of the volume of the aspirated fluid disclosed that the dogs with isolated tricuspid insufficiency produced quantities of ascitic fluid varying from 1.42 L. to 3.20 L. per two weeks (Table III). Production was sustained in one animal for fourteen weeks before spontaneously relenting and in another (Dog 12) a chronic progressive ascites has persisted for more than 200 days (Table I and Fig. 2). The volume of ascitic fluid production at the rate defined did not vary constantly with the fate of the ascites nor with the duration of the animal's survival (Tables I and II). The ascitic fluid was occasionally grossly bloody, but its protein and electrolyte content were not unusual.[9]

TABLE III. ASCITIC FLUID PRODUCTION IN DOGS WITH ISOLATED TRICUSPID INSUFFICIENCY*

DOG NUMBER	ASCITIC FLUID PRODUCTION (PER TWO WEEKS) (ML.)
8	1,421
12	2,715
14	3,198
20	3,000†
19	Ascites spontaneously relented; no periodic paracentesis

*Measured after periodic paracentesis at two-week intervals.
†Ascitic fluid measured at necropsy; this was the only paracentesis performed.

Ascitic fluid production and evaluation of hepatic function with rose bengal dye: The results derived from the bromsulphalein test as used here were unequivocally normal. Among 4 normal dogs and 4 dogs with ascites secondary to tricuspid insufficiency, no measurable quantity of the dye was retained in the serum thirty minutes after injection. In 18 normal dogs, 57.1 ± 7.1 per cent of rose bengal dye was removed from the plasma six minutes after the intravenous injection of 40 mg. In 12 ascitic dogs, including animals with isolated tricuspid insufficiency and others having the valvular lesion combined with large arteriovenous fistulae,[11] only 46.3 ± 9.4 per cent of rose bengal dye was excreted from the plasma after six minutes. The quantity of the dye retained in ascitic dogs is significantly higher than that measured in normal dogs ($P < 0.01$), an observation which suggests an impaired hepatic function in some

of the ascitic animals. There does not appear to be a constant correlation between liver function, as evaluated by the rose bengal dye method, ascitic fluid production, and concentration of plasma proteins in these ascitic dogs.

Alterations of Peripheral Venous Pressure in Experimental Ascites.—This study demonstrated that, once a satisfactory technique of measurement was acquired, the changes in venous pressure rather consistently indicated maximal elevations within the jugular and femoral veins concomitant with the development and progression of the ascites and substantial declines in pressure following paracentesis. The pattern of the waxing and waning peripheral venous pressure in an ascitic dog is illustrated in Fig. 3. During the interval

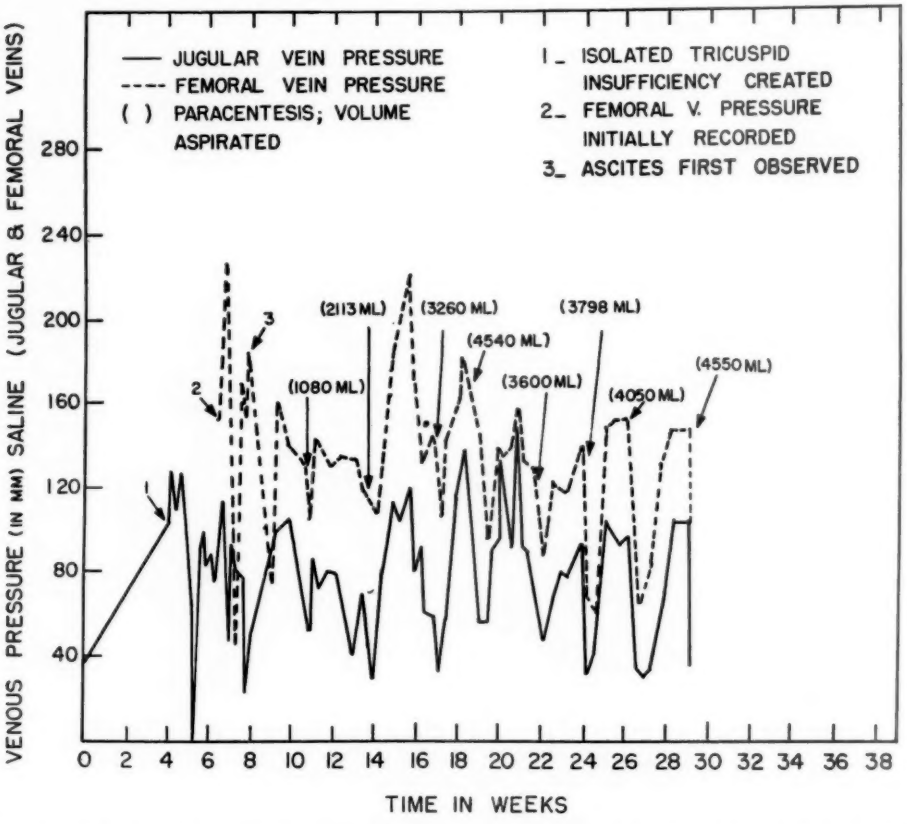

Fig. 3.—Peripheral venous pressure alterations in an ascitic dog with isolated tricuspid insufficiency (Dog 12).

immediately preceding the employment of paracentesis, as indicated in Fig. 3, ascitic fluid accumulation was maximal. In contrast, the intervals immediately following paracentesis were characterized by absence of demonstrable ascites for variable periods and greatly diminished venous pressure. Dogs with isolated tricuspid insufficiency and transient, relenting ascites demonstrated significant venous hypertension (260 mm. of saline, femoral vein) which declined substantially with the resolution of the ascites. Throughout the approximate three months of survival which followed the spontaneous absorption of the

ascitic fluid in Dog 19 (Table I), the venous pressure was stabilized (100 to 140 mm. saline, femoral vein) but did not approximate the preoperative level of 50 mm. saline.

Liver, Adrenal, and Heart Weights in the Ascitic Dogs.—At necropsy examination the outstanding gross pathologic change in the ascitic dogs was the marked hepatic congestion. This is reflected by the augmented weight of the liver (Table IV), which was more than twice the normal proportion of liver weight to total body weight despite the enhancement of the latter by substantial increases in the extracellular fluid volume. The adrenal gland weight in proportion to the body weight of the ascitic dog was inconstant, but the weight of the hearts in the animals which expired did not demonstrate appreciable alterations. Descriptions of the histologic study of these specimens will be reported elsewhere.

TABLE IV. WEIGHT OF THE LIVER IN ASCITIC DOGS WITH ISOLATED TRICUSPID INSUFFICIENCY*

DOG NUMBER	WEIGHT OF LIVER (GM.)	WEIGHT OF LIVER (GM. PER KG. BODY WEIGHT)	WEIGHT OF LIVER† (PER CENT OF BODY WEIGHT)
8	1,815	134.4	13.44
10	2,230	91.4	9.14
14	755	63.7	6.37
20	982	46.5	4.65

*Mean weight of liver in normal dog = 3.8 per cent of body weight.[12]
†Mean weight of liver in ascitic dogs = 8.4 per cent of body weight.

Variations in the Experimental Ascites and Duration of Survival.—Despite the conformity in the anatomic defects produced, the resulting isolated tricuspid insufficiency was associated with a considerable variation in the severity of the ascites and the duration of survival (Table I).

Only 2 of 7 dogs with less than total defunctionalization of the tricuspid valve developed even a transient ascites. In one of these (Dog 10), ascites with other evidence of congestive cardiac failure was demonstrable only at necropsy (Table I). Four of the 5 animals with severance of virtually all of the chordae of the tricuspid valve developed grossly demonstrable ascites and in only one did the ascites relent during the period of observation. In one animal (Dog 12) the ascites has been of progressive severity for 7 months (Fig. 3, Table I). Two of these 5 severely ascitic dogs with total tricuspid incompetence died in congestive heart failure; one on the sixteenth postoperative day, the other on the fortieth day after operation (Table I).

DISCUSSION

Early interest in tricuspid insufficiency arose from the clinical concept enunciated by Durosiez and later by others, which proposed that the development of functional tricuspid regurgitation in patients with intractable left heart failure was followed by resolution of pulmonary edema and dyspnea.[13] The conviction that tricuspid incompetence provided a mechanism for decompression of the pulmonary circuit was the rationale for the creation of an artificial tricuspid insufficiency in patients with mitral stenosis or left ventricular failure for whom more direct surgical intervention was not feasible.[14]

Most of what is known of the dynamic circulatory changes secondary to tricuspid insufficiency has been derived from experimental studies since the occurrence of isolated tricuspid insufficiency in patients is rare. The description by McCord[15] of the right atrial pressure changes in four patients with tricuspid insufficiency presents one of the few clinical evaluations.

There appears to have been no thorough effort to determine the limits of tolerance of the canine heart for isolated tricuspid insufficiency and presumably, because of this, no experimental demonstration that a protracted syndrome simulating severe right heart failure with ascites could be induced by this defect. Indeed, the limited valvular insufficiency produced experimentally by others has been determined in part by the specific interest of the investigator and the design of the operative approach.

Most investigators have employed ingenious blind or closed surgical techniques for the production of tricuspid insufficiency in dogs. Mezei and his associates[16] utilized a Cournand catheter with a rubber sac attached at the extremity. When the device, with balloon inflated, was withdrawn from the right ventricle into the atrium, varying numbers of the chordae tendineae of the tricuspid valve were ruptured. Cassio and Perianes,[14] as well as Barger and associates,[17] employed a valvulotome which was either passed along the jugular vein or traversed an incision in the right atrium or ventricle. Two direct-vision surgical techniques for producing tricuspid insufficiency have been described. The limitations of the method of Sprafka, Haddy, Alden, and Baronofsky[5] have been alluded to previously. Robicsek and associates employed temporary venous inflow occlusion with right ventriculotomy through which the chordae were severed under direct vision.[10] Our experience demonstrated that if the ventriculotomy was small enough to assure control of hemorrhage, the division of an appropriate number of chordae to effect significant tricuspid regurgitation was a most tedious task. The localization of valvular incompetence to a specific cusp or cusps with this approach is virtually impossible. The use of ventriculotomies of greater length usually required concomitant temporary occlusion of the venous inflow to avoid excessive blood loss. The problem here is magnified by the necessity to effectively close the ventriculotomy before the inflow stasis is released, since large incisions which traverse the ventricular wall are difficult to approximate securely by the usual technique of crossing temporary stay-sutures. Under the circumstances the duration of inflow occlusion required to create significant tricuspid incompetence and to suture the ventriculotomy may be intolerable. Whereas a normal dog may endure total vena caval occlusion for five minutes,[18] the experiences cited here suggest that the tolerance of the canine heart to venous inflow stasis is diminished, at least during the immediate interval which follows the production of severe tricuspid insufficiency by the method described.

Halmagyi[19] has contributed an excellent analysis of the physiologic alterations in dogs effected by isolated tricuspid insufficiency produced by the methods of Mezei[16] and Robicsek.[10] He demonstrated that, for the development of the characteristic signs of tricuspid insufficiency, there must exist functional incompetence of at least two cusps. Among this latter group, which he desig-

nated "severe" tricuspid insufficiency, the essential alterations in circulatory dynamics included pulmonary hypertension, augmented pulmonary resistance, an elevated cardiac index, and a diminished renal plasma flow.[19] Despite significant increases in right atrial pressure with associated gross and microscopic evidence of hepatic congestion, neither ascites nor heart failure occurred in Halmagyi's study. Barger elicited enormous increases in already elevated right atrial pressures through exhausting exercise of dogs with tricuspid insufficiency, but none of the animals demonstrated evidence of cardiac decompensation. The record of these experiences ostensibly supported the observation that only rarely does an isolated valvular lesion progress to congestive heart failure.[17] This appears to be further substantiated by the reports which describe the production of experimental heart failure and/or ascites in dogs by combining tricuspid insufficiency with pulmonary stenosis.[5, 17]

The results of this study demonstrate that isolated tricuspid insufficiency can be productive of manifest ascites and cardiac edema if the valvular incompetence is appropriately severe. Under circumstances where isolated tricuspid insufficiency is inadequate, the ability of supplementary circulatory stresses to provoke ascites and cardiac failure may possibly be related to increased sodium and water retention or to an augmented cardiac work burden.[11, 20]

Our observations on the fluctuations in peripheral venous pressure suggest the need for a further analysis of venous hypertension as a pathogenetic mechanism in ascites. The uniformity of the grossly advanced hepatic congestion makes it difficult to evaluate this in relationship to the elevation of venous pressure or to the severity of the ascites.

Since rose bengal dye is quantitatively excreted by the liver, Delprat's report[6] that less than 50 per cent of a given dose of the dye is retained in the plasma of normal human subjects after six minutes provides a useful standard for evaluating hepatic function. These results and the values derived from normal dogs here are entirely comparable. The contrasting data obtained from the use of the dye in ascitic dogs suggests that the method may be applicable in estimating impairment of hepatic function under these experimental conditions.

SUMMARY

The canine heart has an enormous tolerance for isolated tricuspid insufficiency created by division of the chordae tendineae of the valve. Total or virtually complete defunctionalization of the tricuspid valve consistently resulted in a grossly severe ascites, although its fate was variable. The operative method employed here assured that surgical manipulation was performed under direct vision and provided a useful experimental animal with a precisely reproducible anatomic defect.

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RESULTS OF SURGICAL TREATMENT OF CANCER OF THE TONGUE

ARNOLD J. KREMEN, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota and the Division of Surgery Mt. Sinai Hospital)

HISTORICALLY, cancer of the tongue was one of the first cancers to be treated surgically, the first attempt having been made as early as 1664 by Marchetti.[12] Today this lesion still poses a pressing therapeutic problem since it is the cause of more deaths than any other cancer of the head and neck area. Many of the surgical techniques that have achieved popular usage today were first explored by European pioneers of surgery. Among those who deserve special mention are Regnoli,[16] Billroth,[2] Kocher,[8] Chaissaignac,[5] Syme,[18] Butlin,[3] and Trotter.[19] As a result of their efforts it became apparent that control of the primary site of involvement alone did not insure a cure, as many patients subsequently succumbed to cervical glandular involvement. Butlin, and later Trotter, postulated that therapy directed to the glands should be as much a part of the plan of management as removal of the local lesion. Crile[6] in 1906 described the technique of radical neck dissection which clearly defined the principle of resecting en masse all of the lymphatic-bearing tissues of the neck. For control of metastatic cancer to the cervical lymph glands, this technique and its subsequent modifications and refinements has achieved wide acceptance and usage.

Because of technical difficulties with maintaining an adequate airway, crude anesthesia, inability to cope with blood loss, and with the ever-present threat of infection, the results of these early efforts to treat primary cancer of the tongue surgically were discouraging, unduly mutilating, and often unsuccessful. Following the introduction of radiation therapy for cancer there were no staunch advocates of surgical treatment and the care of these patients was left, for the most part, to the radiotherapist.

In the past ten years, aware of the shortcomings of irradiation therapy and stimulated by advances in ancillary surgical techniques, anesthesia, blood replacement, and, most important, antibiotics to control infection, interest in radical surgery for intraoral cancer was reawakened. It now appeared possible and safe to apply well-established concepts of cancer surgery to this area. Radiation therapy, cautery excision, or conventional surgical excision of the primary lesion in the tongue have all had their advocates. For permanent control of metastatic cancer in cervical lymph nodes broad agreement has been achieved that radical lymph node dissection is the procedure of choice. Heretofore, however, these methods of treatment have been applied in a discontinuous fashion with attention being directed to the cervical lymph glands only after the primary growth had been treated with reasonable assurance of permanent eradication. In 1948 I first embarked on a plan of surgical management of cancer of the tongue which applied classical concepts of cancer surgery to this

area; namely, en masse removal of the primary lesion, intervening tissue, and regional lymph-bearing areas. The operative technique and preliminary results were published in this JOURNAL in 1951.[9] Having described and advocated this plan of management, I feel obliged and obligated to submit the long-term results of this study. To date, 32 patients with primary cancer of the tongue have been treated in this fashion; all have been carefully followed and evaluated and form the basis of this report.

METHOD

All cases of cancer of the tongue seen in the tumor clinic at the University of Minnesota since June, 1948, plus the private cases of the author that were deemed suitable for surgical care, were operated upon as described. Criteria of operability were as follows: (1) The lesion should be confined to one-half of the tongue and/or floor of the mouth and not grossly extended beyond the midline. (2) Lesions arising primarily in the base of the tongue were excluded since these are highly undifferentiated growths and are ordinarily quite radiosensitive. Lesions arising in the middle third of the tongue and extending posteriorly have been included and some resections have been carried as far posteriorly as the epiglottis. (3) Clinical evidence of regional lymph node involvement was not looked upon as a contraindication unless the nodes were massively enlarged, agglutinated, and fixed. (4) Age of the patient was no contraindication if general condition was satisfactory. Six of the patients in this series were over 70 years of age. (5) There should be no evidence of distant metastases.

LYMPH NODE INVOLVEMENT

Opinions have varied as to the advisability of performing neck dissections regularly for cancer of the tongue in the absence of clinical evidence suggesting metastases. Martin and associates[11] have stated that 60 per cent of unselected cases of cancer of the tongue at some time in the course of their disease will metastasize to the regional lymph nodes. However, the same author was able to observe only 22 per cent metastases in early cases which had no clinical evidence of node involvement when first seen. Roux-Berger[15] of the Curie Institute of Paris reported a yield of 46 per cent histologic node involvement when the so-called prophylactic or elective neck dissection was performed in the absence of clinically palpable nodes.

TABLE I.—LYMPH NODE INVOLVEMENT AT INITIAL OPERATION

NODES	TOTAL CASES	HISTOLOGIC CANCER		PER CENT INVOLVEMENT
		POSITIVE	NEGATIVE	
Clinically negative nodes	21	9	12	43
Clinically palpable nodes	11	7	4	64
Total cases	32	16	16	50

Table I shows the results of this group of patients. Of the total group of 32, it was possible to demonstrate deposits of cancer histologically in the resected neck specimen in 16 patients, or 50 per cent. In those patients where the nodes were not palpable preoperatively, 9 out of 21, or 43 per cent, showed histologic evidence of cancer. In the 11 patients where the nodes were palpably enlarged before operation, 7, or 64 per cent, were shown to be involved microscopically. The yield of 43 per cent node involvement in the clinical

negative group strongly supports the thesis that removal of the regional lymphatic-bearing tissue should be an immediate essential part of the management of all operable cases of cancer of the tongue. Moreover, this yield may indeed be considerably higher. These values should be taken as a base-line figure since this material was not serially sectioned, and it is possible that some small tumor deposits may have been overlooked. Saphir and Amromin[17] reported serial section studies in 30 patients whose axillary lymph nodes were removed by radical mastectomy and reported as negative on routine pathologic sampling. By the enormous labor of serial sectioning the specimens, they were able to demonstrate metastatic tumor in ten patients, or 33 per cent of those cases previously reported as negative. Similar findings are being observed by Dr. Lattes[10] and his associates in the Department of Surgical Pathology at the Columbia–Presbyterian Medical Center.

RESULTS

To date, there have been seven recurrences observed in the entire group of 32 patients. One patient developed what is believed to be a new cancer of the mouth twenty-four months after his original operation, the new lesion appearing on the opposite side of the mouth, well away from his primary site. Table II shows the time interval from operation to recurrence. All except one recurred in less than one year. One woman (E. E.) developed a cross-neck metastasis after sixteen months. When cancer of the tongue is treated surgically, recurrences are apparent early since they usually occur in peripheral areas immediately available to inspection and palpation, and distant hematogenous metastases are rare.[13] In this material all clinical cures beyond two years significantly remained free of disease during subsequent follow-up.

TABLE II.—RECURRENCE

PATIENT	TIME FROM OPERATION TO RECURRENCE (MONTHS)	SITE OF RECURRENCE
B. F.	5	Neck
H. R.	8	Residual tongue
G. M.	5	Neck
F. W.	3	Neck
J. R.	10	Base of tongue
E. E.	16	Opposite neck
J. K.	24	Probably new cancer on opposite side of mouth

TABLE III.—THREE-YEAR RESULTS: ALL CASES

		DEAD OR RECURRENCE	ALIVE AND FREE OF DISEASE	
		NUMBER	NUMBER	PER CENT
Total cases	23	8	15	65
Pathologically negative nodes	12	1	11	92
Pathologically positive nodes	11	7	4	36

Table III shows the three-year follow-up of 23 patients treated over three years ago. Of the entire group, 15, or 65 per cent, were apparently cured. Of the 12 patients with histologically negative lymph nodes, 11 were alive and well. In the group of 11 patients with histologically positive lymph nodes

there was one postoperative death from a pulmonary embolus. Of the remaining 10 patients, 6 developed recurrent cancer. Four patients were alive and well after more than three years.

Nineteen patients were treated over four years ago. Thirteen, or 68 per cent, were alive and well (Table IV). Ten patients were treated over five years ago and 7, or 70 per cent, were alive and well (Table V). Among these are 2 surviving patients out of 5 with positive lymph nodes, and 5 surviving patients out of 5 with negative lymph nodes.

TABLE IV.—FOUR-YEAR RESULTS: ALL CASES

		DEAD OR RECURRENCE	ALIVE AND FREE OF DISEASE	
		NUMBER	NUMBER	PER CENT
Total cases	19	6	13	68
Pathological negative nodes	9	0	9	100
Pathologically positive nodes	10	6	4	40

TABLE V.—FIVE-YEAR RESULTS: ALL CASES

		DEAD OR RECURRENCE	ALIVE AND FREE OF DISEASE	
		NUMBER	NUMBER	PER CENT
Total cases	10	3	7	70
Pathologically negative nodes	5	0	5	100
Pathologically positive nodes	5	3	2	40

DISCUSSION

Results of treatment of cancer of the tongue by conventional radiation and surgery reported in the literature are variable. Among the best are those of Cade[4] and Berven[1] who report cures as high as 55 per cent in highly selected, small, early cases treated by radiation. Average results of most clinics reporting all cases suggest cure rates of around 25 per cent.[1, 14] On the other hand, cures in advanced cases with involved lymph nodes rarely exceed 10 per cent.[7] The end results of this series, although not fortified by overwhelming numbers of cases, would seem to justify the continued treatment of operable cancer of the tongue in this fashion.

The operation as described has yielded acceptable cosmetic and functional results. There has been some difficulty with speech in the early postoperative period, but after an interval of adjustment these patients have regained sufficient proficiency to be able to converse satisfactorily. Most who had been gainfully employed were able to return to their previous duties. Similarly the ability to eat and swallow poses a problem in the early postoperative period. With time, however, they have learned to satisfy both their nutritional requirements and their gustatory desires with minor restrictions.

Transection of the mandible to provide the exposure necessary to do an adequate incontinuity operation has not posed any problem. Accurate coaptation of the severed mandible with stainless steel wires placed through drill holes leads to prompt healing of the bone with preservation of the mandibular arch. This technique is designed for routine treatment of cancer of the tongue where

involvement of the mandible is not a consideration. It nicely provides the exposure necessary to do an ample excision. If the lesion invades laterally so that one cannot remove an adequate margin of normal tissue lateral to the growth and spare the mandible, the bone should be sacrificed without question and removed en bloc with the rest of the specimen. This is rarely the case, however, with cancer of the tongue, and in the majority of instances the mandible can be spared, returned, and fixed in position to preserve its function and maintain the contour of the face.

SUMMARY AND CONCLUSIONS

1. Thirty-two patients with cancer of the tongue have been operated upon in the fashion described. Sixteen, or 50 per cent of the entire group had histologic evidence of lymph node involvement. In twenty-one cases without palpable cervical lymph nodes, nine, or 43 per cent, showed histologic evidence of lymph node involvement by metastatic cancer.

2. Of 23 patients operated upon over three years ago, 15, or 65 per cent, were alive and free of disease.

3. Of 10 patients operated upon over five years ago, 7, or 70 per cent, were alive and free of disease.

4. The results of this group of cancers of the tongue treated surgically are sufficiently encouraging to warrant its continued trial and clinical application.

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INCREASING THE SURVIVORS OF CANCER THROUGH ASYMPTOMATIC DIAGNOSIS OF MALIGNANT DISEASE

AN EVALUATION OF SEVEN AND ONE-HALF YEARS' OPERATION OF THE CANCER DETECTION CENTER, UNIVERSITY OF MINNESOTA

CLAUDE R. HITCHCOCK, M.D., PH.D.,* AND W. ALBERT SULLIVAN, M.D.,**
MINNEAPOLIS, MINN.

(From the University of Minnesota Medical School)

THE goal of the Minnesota Cancer Detection Center has been the development of a readily applied, accurate examination procedure which includes internal organs as well as readily accessible external organs. In the absence of more simple serodiagnostic or biologic tests (providing ready detection of single types of cancer, groups of cancers, or malignant processes as a whole), an effort of this kind is the only means whereby malignant disease can be diagnosed in its earliest asymptomatic stages.

Unfortunately, when the diagnosis of a cancer is attendant upon the appearance of symptoms or obvious signs of the disease, 60 per cent of patients are doomed to early death from the cancer within five years after the diagnosis. In addition, only 30 per cent of patients with major forms of cancer have a localized lesion at time of diagnosis; in about 50 per cent of patients the cancer is completely incurable when the diagnosis is first established.

"Cancer detection" implies the finding of malignancies before symptoms or signs herald their presence, as well as diagnosing precancerous conditions. We believe several types of serious malignancy can be identified as such before the usual symptoms and signs appear. The means for this accomplishment is a well-conceived, routine plan of repeated examinations in doctors' offices. More important, the 28 per cent of our population over the age of 45 years who have precancerous conditions can be alerted for close observation or immediate therapy.

METHOD

During seven and one-half years' function, from March 1, 1948, to Sept. 1, 1955, 7,375 men and women were examined at the Minnesota Cancer Detection Center, and 173 cancers were detected and proved with biopsy or surgery (Table I). Treatment has been

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*Assistant Professor of Surgery and University Chief of Surgery at Minneapolis General Hospital. Formerly Director of the Cancer Detection Center.

**Instructor in Surgery, and Director of the Cancer Detection Center. University of Minnesota.

under the direction of the patients' personal physicians. This represents an incidence of cancer found in the detection center of 2.3 per cent, or one cancer for every 42 people examined. The total number of examinations performed is 19,890, and there has been one cancer attributable to detection center practice for every 115 examinations performed. Moreover, 28 per cent of these examinees were found to have a precancerous condition for which prophylactic therapy was usually advised. The precancerous lesions include the following: adenomas and polyps of rectum and colon, gastric polyps, kraurosis vulvae, leukoplakia, pigmented nevi in areas of irritation, polyps of vocal cord, senile keratoses, and thyroid adenomas. It is impossible to calculate the probable salvage in this large group of people (28 per cent) through prevention of malignancy by early application of appropriate therapy during the premalignant stage.

At the time of writing there have been 153 deaths from all causes among the over-all group (2 per cent). Only 54 deaths were due to cancer (0.73 per cent of total number of examinees). For one of many reasons, 1,637 examinees (in addition to persons now dead) have become inactive from the standpoint of yearly return visits for recheck examinations. This group represents 22.6 per cent of the total 7,375 people; however, they are not lost for follow-up (Table II). The total cancer experience in a study of this kind must be known, in order that logical evaluations of accomplishment can be made. These nonactive members are circularized yearly and appropriate record made of any serious illnesses. In the event of a malignancy, the surgeon's operative record and the pathologic slides are obtained for review in the center. To date we have 100 per cent follow-up on all cancer cases found in the detection center, and almost a perfect follow-up for the entire nonactive group.

We have been unable to restrict examinations to asymptomatic people only, since it is obvious that all people have some symptoms during any extended period of time. Therefore, the examinees with malignant disease were separated into asymptomatic, or symptomatic groups. Of the 173 patients found to have cancer during examination in the center, 88 had symptoms referable to the organ or organ system in which the malignancy was detected, and 85 did not have symptoms. We shall attempt to show that survival figures are remarkably better for the asymptomatic group. Table III lists the site of cancers found by the Center, and the number that were in each category.

In Table IV the value of the recheck examination is demonstrated by the fact that 49 per cent of the cancers were found during the second or subsequent examination; of the asymptomatic cancers more (47) were detected on a recheck visit than were found at the first examination (38).

The details of examination procedure have been adequately presented in previous publications[1, 9, 10, 12] and will not be included in this report. However, it should be mentioned that every examinee receives (in addition to a complete physical examination, routine blood and urine examination, and chest roentgenogram) a gastric analysis using a

TABLE I. INCIDENCE OF CANCER FOUND AT CANCER DETECTION CENTER, UNIVERSITY OF MINNESOTA, FROM MARCH 1, 1948, TO SEPT. 1, 1955

Total patients examined			7,375
Men		3,568	
Women		3,807	
Total recheck examinations			12,515
Men		6,469	
Women		6,046	
Total examinations			19,890
Over-all incidence of cancer	(225)	1 in 33	(3.1 per cent)
Incidence of cancer found in C.D.C. examination	(173)	1 in 42	(2.3 per cent)
Incidence of cancers per examination	(173)	1 in 115	

TABLE II. CANCER DETECTION CENTER, MARCH 1, 1948, TO SEPT. 1, 1955

	NUMBER	PER CENT
Total C.D.C. population	7,375	
Number inactive in study (minus deaths) (These members are circularized yearly for follow-up)	1,637	22.6
Total number of dead (all causes)	153	2.0
Men	112	
Women	41	
Total number dead of cancer	54	0.73

TABLE III. SITES OF CANCERS FOUND AT CANCER DETECTION CENTER, MARCH 1, 1948, TO SEPT 1, 1955

SITE		ASYMPTOMATIC	SYMPTOMATIC	TOTALS
Stomach		10	6	16
Colon		14	5	19
Rectum		9	3	12
Small bowel		1	0	1
Skin		7	38	45
Breast		10	4	14
Cervix		9	2	11
Uterus		0	7	7
Ovaries		5	1	6
Prostate		8	7	15
Urinary bladder		1	1	2
Kidney		0	0	0
Thyroid		2	2	4
Lower lip		0	3	3
Floor of mouth		1	0	1
Lymphosarcoma	thyroid	1	0	3
	mesocolon	1		
	stomach	1		
Malignant lymphoblastoma		0	1	1
Hodgkin's disease		1	0	1
Myeloma		1	0	1
Lymphatic leukemia		0	7	7
Lung		3 (metastatic)	1	4
TOTALS		85	88	173

TABLE IV

	ASYMPTOMATIC	SYMPTOMATIC	TOTALS	
			NUMBER	PER CENT
Number of cases detected at first examination	38	50	88	51
Number of cases detected at recheck examinations	47	38	85	49

Levin tube for aspiration of gastric content; a proctosigmoidoscopic examination to 25 cm.; a stool study for occult blood after a three-day meat-free diet; a pelvic examination for women; and Papanicolaou examinations of cervical and vaginal smears as well as any sputum resulting from a productive cough. The physician summarizing the results of examination with the patient determines whether or not further roentgenographic study is needed according to the following plan:

A gastrointestinal series is ordered in cases with the following findings: (1) histamine achlorhydria and hypochlorhydria (less than 30° free acid); (2) occult blood in the stool; (3) family history of gastric carcinoma; (4) unexplained hemoglobin level of less than 11 Gm.; (5) vague gastric symptoms which in any way could be interpreted by the ex-

amining physician as being due to gastric carcinoma; (6) any evidence of undue weight loss. The air-contrast technique is helpful in cases of suspected gastric polyps or small mucosal defects.

Roentgenograms of the colon (barium enema) are indicated in the presence of the following: (1) abnormal findings on proctoscopic examination; (2) occult blood in the stool; (3) unexplained hemoglobin level of less than 11 Gm.; (4) family history of malignancy of the large bowel; (5) vague symptoms which could be interpreted by the examining physician as being due to malignancy of the large bowel; (6) undue weight loss (10 pounds or more). In addition to routine barium enema roentgenograms, all patients found to have polyps are studied by means of air-contrast barium enemas.

Intravenous pyelograms are ordered for patients with the following: (1) blood in the urine; (2) costovertebral pain or tenderness; (3) palpable mass in kidney region.

RESULTS

Relative Incidence of Cancer Detection Center Malignancies.—One desirable feature of a group such as the detection center population would be a reasonable conformity of the incidence of cancers with the general population in the age range of the study (45 years or over). The possibility exists that, by virtue even of their willingness to participate in a long-range study of this kind, the examinees might represent a markedly deviated segment of the population. Accomplishments would then have lesser significance in terms of practical application and actual experience in the general population.

To validate our results we compared the annual incidence of cancers in the detection center group with similar figures for New York State (detection center study, 1948-55; New York study, 1949-51). Tables V and VI list the prominent sites of cancer for men and women in a descending order of prevalence as seen in New York State; in the column opposite are placed the figures representing the similar arrangement of sites of cancer from the detection center group. A heavy connecting bar denotes a site of cancer for which our incidence was more than two places removed from the New York figures. It is apparent that the only serious disagreement exists for carcinoma of the

TABLE V. COMPARISON OF ANNUAL INCIDENCE OF CANCERS BETWEEN CANCER DETECTION CENTER AND NEW YORK STATE

NEW YORK STATE: 1949-1951	MALES	CANCER DETECTION CENTER: 1948-1955
1	Skin	1
2	Prostate	2
3	Lung	10
4	Stomach	3
5	Colon	4
6	Rectum	5
7	Urinary bladder	11
8	Leukemia	6
9	Pancreas	7
10	Lip	8
—	Lung (metastatic)	9
—	Thyroid	12
—	Lymphosarcoma	13
—	Brain tumor	14

Heavy bar indicates more than 2 position discrepancy.

lung; in New York State it is in third place of descending prevalence for men, and in the Detection Center it is in *tenth place* (Tables V and VI). The overall conformity with established incidence figures indicates an acceptable representation in the detection center group of a similar segment of the general population. It is difficult to explain the paucity of primary bronchogenic and pulmonary cancers in the detection center examinees. No ready explanation has been available.

TABLE VI. COMPARISON OF ANNUAL INCIDENCE OF CANCERS BETWEEN CANCER DETECTION CENTER AND NEW YORK STATE REGISTRY

NEW YORK STATE: 1949-1951	FEMALES	CANCER DETECTION CENTER: 1948-1955
1	Breast	1
2	Cervix	4
3	Colon	3
4	Skin	2
5	Endometrium	5
6	Stomach	6
7	Ovary	7
8	Rectum	8
9	Leukemia	9
10	Pancreas	13
—	Thyroid	10
—	Gall bladder	11
—	Lymphosarcoma	12

Heavy bar indicates discrepancy of more than 2 positions.

Recent studies by one of us (C. R. H.) indicate that the incidence of lung cancer in the major metropolitan area of Minneapolis and St. Paul is almost identical to that in other cities, and the country as a whole. Moreover, careful analysis of the smoking habits of the people we studied indicates that only 15 per cent of the women smoke (7 per cent of these classed as heavy—20 or more cigarettes daily) and 81.4 per cent of the men smoke (21.4 per cent of these classed as heavy). Among the men 45 per cent inhaled and 64 per cent were predominantly cigarette smokers. It is apparent that absence of primary lung cancers in our group (2 up to this time) is not owing to abstinence from the use of tobacco, at least among the men.

Analysis of Total Group of Cancers.—It is inevitable that some cancers will appear under circumstances precluding their consideration as detection center pickups. Of the total cancers recorded for the detection center group (225 cancers), 173 malignancies are considered as having been detected by the center, and 52 malignancies are not. In Table VII we see a breakdown of the latter group into (1) cancers in patients who were without positive findings during examination, but in whom a lesion appeared after 2 months had elapsed between rechecks (27 cancers—12 per cent of total); (2) cancers not diagnosed in the center because of failure on the part of the patient to cooperate with our recommendations (14 cancers—6.2 per cent of total); and (3) cancers frankly missed during the detection center examination and which were diagnosed by the family physician within two months after our negative examina-

tion (11 cancers—4 per cent of total). For purposes of further evaluation of mortality rates the latter three groups are lumped together and considered "cancers not diagnosed in the Detection Center." This group of cancer cases (52) represents 23 per cent of the over-all number of cancers.

From Tables VIII, IX, and X it is apparent that the mortality has been high in these cases (52 per cent mortality so far). It should be noted, however, that this group includes 5 patients with cancer of the pancreas, 2 patients with cancer of the gall bladder, and 2 patients with cerebral lesions, all of whom have died of their disease. Malignancies in these sites are uniformly hopeless of early diagnosis under present methods except in very rare circumstances, or under conditions of fortuitous incidental discovery.

Further analysis of these categories shows that, if "patient's failure to cooperate" is excluded, the over-all detection center accuracy has been noteworthy. Sixteen per cent of the 225 known cancers represent failure of examination methods, and only 4.8 per cent were missed because of error by the examining physician. Of the 173 cancers correctly diagnosed, 42 were established by roentgenograms of one kind or another. Only 3 of the frankly missed cases were dependent upon x-ray methods for diagnosis, and this constitutes 7.1 per cent failure for roentgenologic diagnosis during the seven and one-half years of operation of the Center. This figure compares favorably with diagnostic experience in the radiology department at the University of Minnesota Hospitals, especially when we realize that the total number of roentgen examinations of all types now totals almost 100,000 for this group of people. All roentgenologic diagnostic methods have specific limitations and clinicians responsible for patients must seek to bring other more specific methods (cytologic techniques, tissue examination, and so forth) to bear in questionable cases.

Of the cancers correctly diagnosed, 131 were found either during physical examination or by means of laboratory study. If we consider 23 of the missed lesions as failures of physical diagnosis or laboratory methods, this

TABLE VII. OVER-ALL INCIDENCE OF CANCER AMONG 7,375 PERSONS EXAMINED

	NUMBER	PER CENT OF TOTAL CASES OF CANCER
Total number of cases attributed to detection by C.D.C.	173	77
Asymptomatic cases detected by C.D.C.	85	37.5 of total cancers 49 of C.D.C. cancer pickups
Cases detected in C.D.C. with symptoms (in retrospect)	88	39.5 of total cancers 51 of C.D.C. cancer pickups
Cancers not detected by Detection Center	52	23
1. Cancers in patients who were without positive findings during examination, but with lesion which appeared between rechecks	27	12
2. Cancers not diagnosed in C.D.C. due to failure of patient cooperation	14	6.2
3. Cancers frankly missed during examination at C.D.C.	11	4.8

TABLE VIII. CASES IN WHICH PATIENTS FAILED TO RETURN FOR RECHECK OR FOLLOW-UP PROCEDURES AND IN WHICH CANCER DEVELOPED SUBSEQUENTLY

SITE OF LESION	CASES	INTERVAL BETWEEN LAST C.D.C. EXAMINATION AND DIAGNOSIS (MONTHS)	REMARKS
Stomach	4	24; 63; 64; 50	3 achlorhydric; 1 hypochlorhydric; 3 dead
Colon	3	6; 24; 27	2 dead
Breast	2	18; 20	1 dead
Pancreas	2	24; 25	2 dead
Kidney	1	17	Living with symptoms: 3 months
Meninges	1	18	Dead
Tongue	1	16	Dead

TABLE IX. CASES IN WHICH MALIGNANCY DEVELOPED BETWEEN FIRST EXAMINATION AND RECHECK EXAMINATION

SITE OF CANCER	NUMBER OF CASES	STATUS (MONTHS FROM NEGATIVE EXAMINATION TO SYMPTOMS)
Kidney	1	10 months—living 45 months
Gall bladder	2	4-7 months—both dead
Prostate	3	7-8-14 months—2 dead
Corpus uteri	3	10-9-10 months—3 living
Pancreas	3	5-8-14 months—3 dead
Breast	3	9-11-12 months—3 living
Ovary	2	12-14 months—2 dead
Skin	2	4-6 months—2 living
Tonsil	1	10 months—dead
Lymphosarcoma (thyroid)	1	8 months—dead
Melanoma (eye)	1	8 months—living 24 months
Brain (metastatic from melanoma)	1	4 months—dead
Urinary bladder	1	11 months—living 36 months
Metastatic (primary unknown)	1	14 months—dead
Lower lip	1	12 months—living 24 months
Colon (carcinoid appendix)	1	6 months—living 32 months
Total	27	

TABLE X. FAILURES OF DIAGNOSIS DURING CANCER DETECTION CENTER EXAMINATION

SITE OF CANCER	CASES	REMARKS
Colon	2	1 diagnosed diverticulitis by x-ray (dead) 1 missed by x-ray (splenic flexure lesion—dead)
Kidney	1	Lower urinary tract symptoms
Lung	1	Failure of x-ray diagnosis; dead
Skin	5	Failure of examining physician to recommend biopsy proof (1 dead of coronary disease)
Breast	2	Nodule missed on physical examination
Total	11	

represents 14.5 per cent inaccuracy as far as missing malignancies are concerned. Many lesions, however, were reported as suspicious (prostate, breast, ovary, thyroid) and proved to be benign. Again, the necessity for definitive histologic and cytologic verification is imperative.

Comparison of Mortality Rates.—Table XI shows the mortality rates for the various groups of cases during the seven and one-half years. Since all skin lesions in the detection center examinees have been early lesions, and no deaths or serious recurrences have occurred, we have excluded cancer of the

skin from the calculation of mortality percentages. This omission, from each group under consideration, leaves only major forms of cancer for this comparison.

TABLE XI. OVER-ALL MORTALITY RATES

	NUMBER OF DEATHS	PER CENT
Deaths in *asymptomatic* group minus skin cancers (78 cases)	14	18
Deaths in *symptomatic* group minus skin cancers (50 cases)	17	34
Deaths among patients not diagnosed at Detection Center minus skin cancer cases (47 cases)	27	58
Deaths in total group of cases detected at Cancer Detection Center (173 cases)	31	18
Deaths in total group of cases (225 cases)	58	25.8

TABLE XII. COMPARISON OF CANCER DETECTION CENTER SURVIVALS

ORGAN	ASMYPTOMATIC		SYMPTOMATIC†		NATIONAL 5-YEAR SURVIVAL (PER CENT)
	LIVING* (PER CENT)	MEAN SURVIVAL (MONTHS)	LIVING* (PER CENT)	MEAN SURVIVAL (MONTHS)	
Stomach	10 70	36.3 (1 over 5 years)	10 20	26	5-7
Colon	14 93	47 (6 over 5 years)	11 36	54 (2 over 5 years)	20-25
Rectum	9 78	40 (3 over 5 years)	3 33	55	10-16
Breast	10 90	47 4 over 5 years)	11 90	28 (1 over 5 years)	35-46
Cervix	9 88	35 (2 over 5 years)	2 100	47.5	30-35
Uterus (endometrium)	—	—	10 100	20	40-50
Ovaries	5 40	33 (1 over 5 years)	3 33	48	20-30
Prostate	8 75	15	10 70	42 (2 over 5 years)	7-15
Skin	7 100	46 (3 over 5 years)	45 100	39 (8 over 5 years)	75-85
Chronic lymphatic leukemia	—	—	7 43	69 (2 over 5 years)	10-15
Lymphosarcoma	3 100	31	1 0		20-25

*Small number in upper left-hand corner indicates total cases in that group.

†Cases of cancer not diagnosed in the Center are included here since they were all symptomatic at time of diagnosis.

There were 27 deaths among the 47 cases of cancer not diagnosed at the center, a mortality rate of 58 per cent. In comparison, in the symptomatic group of cancers found during examination at the Center, the mortality rate

is 17 deaths in 50 cases, or 34 per cent. In the asymptomatic group there were only 14 deaths among 78 cases, or a mortality rate of 18 per cent. The pronounced improvement in the over-all reduction of cancer mortality is clear cut when serious cancers can be detected and treated before symptoms or signs develop.

Evaluation of Survivors of Cancer in the Detection Center.—After only seven and one-half years' operation of the Detection Center it is impossible to assess accurately the potential increased salvage of life over and above that normally seen in the general population among persons of the same age group and afflicted with similar malignancies. However, some kind of comparison would be useful and informative regarding possible changes necessary in our operation. Since the number of cases of cancer found during the first two and one-half years of operation is necessarily small (approximately 30), even though they can be evaluated as five-year results, some other means of comparison seemed advisable. Consequently the survival time (in terms of months of survival after diagnosis was established) has been determined for each patient still alive and well following therapy for cancer. The mean survival time for the various sites of cancer has been calculated and entered in Table XII. In order to permit our results to be gauged in some degree at this time, a comparison has been drawn with national five-year survival rates. These latter figures are rather hard to assemble, but cross checking with numerous authors has provided a reasonably accurate set of values.

Gastric cancers: In Table XII we note the surprising fact that 70 per cent of the gastric cancer patients, free of symptoms when their lesion was found and treated, are alive and well with a mean survival time of 36.3 months. This is contrasted with a 20 per cent survival in the patients with gastric cancer who had symptoms relative to the upper gastrointestinal tract when diagnosis was established; the national over-all five-year survival rate for gastric cancer is not over 7 per cent. This accomplishment seems highly important at this time.

A study of the stomach cancer cases reveals that only 3 of the 10 asymptomatic cases had positive lymph nodes (30 per cent) whereas 90 per cent of the 10 symptomatic cases had positive nodes at surgery. Only 10 per cent of the asymptomatic cases had local extension beyond the stomach, but 90 per cent of the symptomatic cases had local extension of the lesion.

Furthermore, all of these asymptomatic patients would have been picked up by using the screening factor of achlorhydria or hypochlorhydria to indicate the necessity for routine gastric roentgenograms in any given patient. Only one patient was possibly delayed one year in the establishment of a diagnosis by gastrointestinal roentgenograms when he showed a normal gastric analysis response between two determinations definitely in the hypochlorhydric range. No gastric cancers have developed in the normochlorhydric portion of our detection center population (75 per cent) as far as we can

determine at this time. Achlorhydria or hypochlorhydria emerges as the most significant criteria indicating the need for roentgenographic study of the upper gastrointestinal tract in cases of early, asymptomatic gastric cancer. We can demonstrate that, in the 25 per cent of the detection center population that is either achlorhydria or hypochlorhydric, there is, respectively, a 3.2 times and 2.3 times risk of development of gastric cancer than in the population of similar age but with normal gastric acidity.[11]

Colon and rectal cancers: A comparison of the survival rates in Table XII for colon cancer demonstrates a 93 per cent survival for the asymptomatic cases, a 36 per cent survival for the symptomatic cases, compared with a 20 per cent national five-year survival rate. The mean survival times are somewhat higher also for the asymptomatic group (forty-seven months) and for the symptomatic group (fifty-four months). Six of the 14 asymptomatic colon cases have lived free of cancer for over five years since surgery. Sixty-eight per cent of the symptomatic cases had positive lymph nodes contrasted with 30 per cent positive nodes in the asymptomatic group.

Routine sigmoidoscopic examination of the rectum and sigmoid colon has proved to be the most useful screening device for lesions of the large bowel. Patients with an abnormal finding such as adenomas or polyps are studied by barium enema–air contrast technique, and the lesions are recommended to be removed. The results of the detection of asymptomatic rectal cancers are seen in Table XII where 78 per cent of the asymptomatic cases are living and well for a mean period of forty months, and only 33 per cent of the symptomatic cases are alive for fifty-five months. This is contrasted with the national five-year survival of 10 to 15 per cent.

TABLE XIII. COMPARISON OF OVER-ALL SURVIVALS AND MEAN SURVIVALS IN MONTHS

TYPE LESION	NUMBER	LIVING (PER CENT)	MEAN SURVIVAL IN MONTHS
Asymptomatic (85)	71	84	37
Symptomatic (140)	96	68	43

Other cancer survivals: Similarly, as one reviews Table XII, the other sites of cancer tend to show increased numbers of survivors in the asymptomatic group. Undoubtedly as time passes the percentages of patients surviving five years or more will decrease somewhat. The extent of this decrease cannot be prognosticated in any realistic manner. However, review of the cases and consideration of the extent of the cancers at the time of treatment would lead the observer to predict a more rapid decline in the survivors in the symptomatic group than in the asymptomatic group. Re-evaluation four or five years from now may well demonstrate a highly significant improvement in the cases surviving a full five years that are of the asymptomatic type. A summary of the four categories is given in Table XIII, wherein 84 per cent of the over-all number of asymptomatic cancer cases have survived for an average period of thirty-seven months compared with a 68 per cent survival

for an average of forty-three months in the symptomatic cancer cases. These calculations represent over-all results including all sites of cancer (internal, skin, and so forth).

Cancer of the cervix: Cervical carcinoma has been diagnosed in 11 women, 9 without symptoms, and 2 with symptoms at time of examination. Of the 11 cases, only one patient had a completely negative pelvic examination as performed with visual inspection and palpation, and then showed a persistently positive Papanicolaou result. The other 10 women had some abnormality such as small abrasion, small polyp, an easily traumatized cervical mucosa, and so forth, all indicating the need for some further definitive diagnostic procedure, such as punch biopsy or conization biopsy. The results of the 11 cervical carcinoma cases are good at this time, and one would expect these women to do well since the lesions were all in an early stage of development.

Of the total number of positive Papanicolaou smears[14] the 11 cancer cases represent 78 per cent. It is possible that an indeterminate number of the patients for whom the smears were reported as suspicious will eventually prove to have cervical carcinoma. However, it must be emphasized that visual inspection of the cervix with biopsy of any suspicious areas provides an excellent chance of detecting lesions early, particularly when such examinations are repeated annually or semiannually. We are not convinced that positive Papanicolaou smears indicate the unequivocal presence of malignancy, nor that the functional changes so often seen limited to the squamous epithelium alone constitute a truly cancerous change in that stage of maturity. However, we do perform the cytologic examination in hope of adding some small measure of protection for the women patients.

Cancer of the endometrium: Endometrial carcinoma was found in 10 women patients, all of whom had abnormal spotting indicating the likelihood of serious disease. Papanicolaou smears were uniformly negative. Diagnosis was always established by dilatation and curettage. All patients are living and well after surgery with a mean survival of twenty months; several have gone four and one-half to five and one-half years without recurrent disease.

A good screening technique is not yet available to detect early endometrial carcinoma. Uterine enlargement and bleeding, and discharge from the cervical os remain the only useful danger signs.

Cancer of the ovary: Of 117 women who were sent back to their doctors with a diagnosis of suspicious adnexal mass, six proved to have carcinoma of the ovary. Two women, who had negative pelvic examinations on a given examination, were diagnosed and treated for ovarian carcinoma during the yearly examination interval. Five cases were asymptomatic and one had symptoms at the time of diagnosis in the Center. All cases were diagnosed as suspicious adnexal masses by bimanual palpation, and the surgical specimens disclosed early cystadenocarcinomas well limited within the capsule of the lesion. The survival figures here are not impressive, 40 per cent survival with a mean of thirty-three months for asymptomatic cases; 33 per cent with a

mean of forty-eight months for the symptomatic cases; compared with a national five-year survival figure of 20-30 per cent. Pelvic examination is the only method for detecting early ovarian carcinoma, and laparotomy is essential to establish the nature of a pelvic mass. Watchful waiting for signs of increasing size in a pelvic mass in women over the age of 40 is no longer a safe or reasonable course to follow. The present extremely low mortality for laparotomy in trained hands makes intervention in all of these cases increasingly urgent.

Cancer of the breast: Suspicious breast lesions were found in 222 women. Carcinoma was proved at surgery in 14 cases (6 per cent). Ten of these malignant nodules were unknown to the patient at time of detection in the Center. This represents 4.5 per cent of all women with a suspicious breast mass to have a so-called "incidental" pickup of a carcinoma. It is difficult to draw useful conclusions regarding survival of these patients due to the protean biologic behavior of breast cancers. Only long-term follow-up will be of real significance. However, there are 90 per cent survivors for a mean of forty-seven months in the asymptomatic group, and 90 per cent survivors for a mean of twenty-eight months among the symptomatic group. The over-all five-year survival rate nationwide is approximately 35 to 45 per cent.

Currently we are studying the usefulness of soft-tissue roentgenograms of both breasts taken in two projections. It is hoped that very small, nonpalpable lesions can be detected, possibly indicating the advisability of removal of the quadrant of the breast harboring such a lesion. Gershon-Cohen and associates[19] have reported some value of this technique, and it should receive a thorough trial.

Cancer of the prostate: Suspicious prostatic nodules were noted in 101 men. Resection or biopsy of the lesion was performed in 25 and carcinoma was proved histologically in 15. We have accepted only frank histologic proof of malignancy, not clinical impression, even though the gland itself may be classical and metastases present. Ten patients have been treated by their physicians for prostatic carcinoma on clinical evidence alone.

Three men were found to have prostatic cancer on examination by their own physicians between recheck examinations at the Center. Symptoms of urinary obstruction, and so forth, developed and were responsible for the patient's seeking help. A highly reliable chemical or biologic test for prostatic cancer is eagerly sought. The alkaline and acid phosphatase determinations are, unfortunately, of no help, since spread beyond the capsule is present before acid phosphatase values rise. Fractional phosphatase methods are currently under investigation elsewhere which might prove valuable. It is only conjectural to assume that repeated examination can significantly alter the outcome of prostatic cancer; in so many instances the malignancy is present, but relatively inactive in the body for prolonged periods of time. In all too many cases, bony metastases are already present by the time the lesion can be definitely palpated, or urinary symptoms signal that the cancer is present.

Cancer of the skin: Skin cancer was diagnosed in the Detection Center in 45 patients. Ten lesions were squamous-cell carcinomas, and 35 were basal-

cell carcinomas. One pigmented nevus, out of 330 reported chronically irritated, proved to be a malignant melanoma. All of the skin lesions were small and localized. Treatment has been successful to the extent that there have been no recurrences, and all of the patients are living and well at the present time. Most patients (38) were aware of the lesion but considered it benign and of no consequence.

Senile keratosis is considered a precancerous condition, and it was noted in 436 instances. The 100 per cent survival noted in Table XII for both the asymptomatic and the symptomatic group (mean of forty-six months and thirty-nine months, respectively) is not difficult to achieve when the physician has the opportunity of treating all skin cancers in their very earliest stages. Definitive diagnosis of any skin cancer depends on histologic examination of tissue, and biopsy should be the stock in trade for every physician in this regard.

Lymphatic system cancers: Chronic lymphatic leukemia was found in 7 patients, and all had symptoms of the disease at time of detection in the center. Presence of a palpable mass, pain or weakness, and elevation of the lymphocyte count were noted. Of 113 cases with a lymphocyte count elevated more than 45 per cent, 107 have not had further evidence of lymphoma up to the present. The survival of the leukemia patients is 43 per cent with a mean of sixty-nine months. This compares favorably with the national survival figures of 10 to 15 per cent five-year survivals.

Comparison of Types of Malignancy Successfully Detected and Those Not Successfully Detected.—It becomes apparent that we can, through vigorous application of a routine and standardized examination procedure, embodying specific screening techniques, successfully detect early cancers in the asymptomatic stages of growth for the following organs: stomach, colon, rectum, breast, cervix, skin, thyroid, and lip.

Results from our Detection Center indicate success with these organs. Perhaps we should add to this group: lung, oral cavity, and prostate. Certainly the ease of performing roentgenographic examination of the lungs places neglect of this screening method on factors of economics and personal antagonism. To the best of our knowledge we are not "missing" lung cancers; they have not been present in as large a percentage as would have been expected. Current reports emphasize the value of thoracotomy for silent lung nodules and surgical removal of those found to be carcinomas.

The ease of inspection and palpation of the oral cavity assures a good chance for early diagnosis of cancer of the tongue, floor of mouth, and so forth, if routine examinations are carried out. Our results for prostatic cancer are probably impressive enough at this time to warrant inclusion in this group. However, further evaluation several years from now may indicate removal to the following category.

In comparison, the results from our Detection Center indicates a failure on our part to screen adequately for, or detect, cancers in the following organs: pancreas, gall bladder, kidney, central nervous system, and ovary.

However, the lesions that can be successfully handled in the Cancer Detection Center constitute the majority of cancers in the population in terms of gross number of cancer cases. This fact increases the significance of the accomplishment of an improvement in survival rates, and the over-all survival rate increases appreciably. On the basis of our results we believe the following prognostication is warranted. If the majority of cancers appearing in the people during each year, in a given state, could be detected in the asymptomatic stage of the disease through mass participation of the population in a yearly Cancer Detection examination program, the over-all five-year survival rate for cancer could be raised from the current 30-33 per cent to 70 or 75 per cent. If only this could be accomplished within one lifetime!

SUMMARY

1. During seven and one-half years' operation of the Cancer Detection Center at the University of Minnesota, 173 cases of cancer were found during a total of 19,890 examinations performed on 7,375 people. This represents one cancer for every 42 people examined (2.3 per cent), and one cancer for every 115 examinations performed.

2. Of the persons found to have cancer, 85 were symptom-free with regard to the organ or organ system in which the lesion was found. In 88 cases the patients had symptoms indicating a likelihood of cancer in the organ or organ system involved. In the asymptomatic group, 47 cancers (55 per cent) were found at recheck examination, indicating the value of repeated examinations to detect early malignancy.

3. Only in cancer detection centers or cancer prevention clinics are large numbers of persons surveyed for cancer while they are without symptoms of disease. This study offers a unique opportunity of comparing the survival rates between symptomatic and asymptomatic examinees found to have cancer.

4. Comparison of the annual incidence of cancers in the detection center population (45 years of age and over) with annual incidence figures for New York State reveals a striking similarity except for carcinoma of the pancreas in women, and carcinoma of the lung and urinary bladder in men. Lung cancer was in tenth place of descending incidence in the Detection Center compared with third place in the New York State figures. No ready explanation can be found for this discrepancy.

5. The survival rate of patients with asymptomatic gastric cancer is 70 per cent, compared with a 20 per cent survival rate among those patients with gastric cancer who had symptoms of the disease at time of diagnosis (mean survival of thirty-six months and twenty-six months, respectively). The national five-year survival rate does not exceed 7 per cent.

6. Cancers of the colon have been detected in a satisfactory manner by using abnormal proctosigmoidoscopic findings as the indication for barium enema–air contrast roentgenograms. There is a 93 per cent survival for a mean of forty-seven months in the asymptomatic group, and a 36 per cent

survival for a mean of 54 months in the symptomatic group. Six of the 14 cancer patients in the asymptomatic group have lived free of cancer for over five years.

There has been a 78 per cent survival of asymptomatic rectal cancer cases, with a mean of forty months, and a 33 per cent survival for a mean of fifty-five months in the symptomatic group. These are compared to a five-year survival rate of 10 to 15 per cent for rectal cancers.

7. Of the total group examined, 28 per cent had precancerous lesions. The value of early treatment for these lesions is incalculable.

8. Of 225 cancers either detected in the Detection Center, or during an interval recheck examination by the personal physician, 23 per cent are considered not to be creditable to the detection center function. Roentgenologic techniques failed in 7.1 per cent of the 42 cases in which diagnosis was established by this modality. Misinterpretation of x-ray changes was the responsible factor. Of the cases detected by means of physical examination and laboratory studies (131), 14.5 per cent must be considered failures for these methods.

9. There were 27 deaths among the 47 patients in whom the malignant lesion was not detected in the Center for one of several reasons (58 per cent mortality). This mortality figure contrasts with a 34 per cent mortality among patients with major cancers in the symptomatic group detected at the center. The asymptomatic group shows only an 18 per cent mortality rate. These calculations were made after eliminating cancer of the skin in each category.

10. We believe that several prevalent types of serious malignancy can be identified in advance of their usual signs and symptoms through the application of a well-conceived, routine cancer detection examination performed annually.

Dr. Wangensteen was the prime mover in the initiation of the cancer detection research program at the University of Minnesota.

The detection center was formally opened on March 1, 1948, under the able leadership of Dr. David State (then associate professor in the Department of Surgery), and was guided during 1951 and part of 1952 by Dr. T. Brannon Hubbard (then assistant professor in the Department of Surgery). The detection center owes a large measure of its success to the untiring efforts of these two directors during the difficult formative years of the project.

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THE TREATMENT OF PRIMARY AND METASTATIC CANCER OF THE LIVER

IRVING M. ARIEL, M.D., NEW YORK, N. Y.

(From the Pack Medical Group)

INTRODUCTION

IT IS A signal honor to participate in this symposium honoring Dr. Wangensteen. It is fitting to discuss the problems of treating liver cancer on this occasion, for Dr. Wangensteen is one of the pioneers in liver surgery. His surgical removal of the right lobe of the liver for cancer has paved the way for developing surgical measures for resecting most localized liver cancers. Although primary liver cancer is not common here (2.5 per cent of all cancer in the United States and 1.2 per cent of all cancer in Europe), in certain parts of the world (among the Bantus) it represents one of the most frequent forms of cancer.[6-8]

Metastatic cancer to the liver is of course a most frequent occurrence and metastases are present in the liver in from 50 to 75 per cent of people who die from cancer.

The Natural History of Liver Cancer.—Primary liver cancer often grows rapidly and usually kills quickly. A short life expectancy is emphasized by the observations of Gustafson,[22] whose patients survived an average of 3.2 months, and Berman,[8] whose patients survived an average of 4 months. Some with a more differentiated form of hepatoma may live much longer.

Primary liver cancer in the human tends to remain limited to the liver rather than grow directly into contiguous structures. Metastasis by way of lymphatics is not common. Blood-borne metastases by any one of the circulatory systems of the liver may result in metastases anywhere in the body, especially the lungs. Metastases to bones are rare, only 16 having been reported and only one severe enough to produce anemia. Thus, anemia in a patient with liver cancer is usually the result of hepatic dysfunction.

It is difficult to evaluate the natural history of a given hepatic metastasis because of the vagaries of growth pursued by different metastases. It has been reputed that metastases in the liver will grow more rapidly than the primary neoplasm. Although this may occur, there are many instances where a prolonged period (from four to five years) elapses before a given hepatic metastasis will become clinically evident. Attempts to judge the growth characteristics of metastases gleaned from autopsy statistics are misleading because these represent the end-stages of the growth pattern. The observations from the "second look" operation as practiced at the University of Minnesota will fill an important hiatus which exists between observations about metastases to liver as observed at the operating table and that at the autopsy table. The author has carefully observed ten patients who had been operated upon for cancer of the rectum or colon and who were found to have

metastases to the liver at the time of operation. No therapy was given to the liver metastases. The average duration from the time of the removal of the primary cancer until the metastatic deposit became clinically evident was four and one-half months. The average duration of life was six and one-half months, and varied from two to ten months. Extremes of growth of metastases occur. In some instances they may grow rapidly and kill within two to four months after occurrence, while in others many years may elapse before symptoms become severe or death intervenes.

The following discussion will present a progress report of studies being pursued at the Pack Medical Group, in which Drs. George Pack, Theodore Miller, David Molander, George Higgins, and I are participating.

DIAGNOSIS OF LIVER CANCER

Before therapy can be instituted it almost seems trite to state that a diagnosis must be made, and it must be made early in the course of the particular growth, if treatment is to be effective.

There are no distinguishing symptoms or signs of early liver cancer or any which help to differentiate between a primary tumor of the liver and one that is metastatic, except possibly a history of treatment for a previous tumor or the presence of another primary tumor elsewhere. Various laboratory procedures have been championed by different authors as diagnostic of the presence of a liver tumor. Before evaluating some of these procedures a generalization may be made to the effect that, in the ultimate analysis, no laboratory tests can be considered specific enough to diagnose the presence of a liver tumor. The Bromsulphalein test and the serum alkaline phosphatase appear to be the best liver function tests to help diagnose liver cancer. In a study performed on the Surgical Service of the University of Minnesota by Dr. Donald Shahon and myself, assisted by Dr. Fred Hoffbauer, it was determined that patients with gastrointestinal cancer presented evidence of hepatic dysfunction regardless of whether or not hepatic metastases were present. The determination which appeared most sensitive to hepatic alteration was the Bromsulphalein excretion which was abnormal in almost 50 per cent of the patients studied. Since the Bromsulphalein test was found to be most sensitive, an attempt to correlate this with hepatic metastases revealed no relationship. In four patients with hepatic metastases the Bromsulphalein test was abnormal while in four others the Bromsulphalein test was normal. In five patients with gastrointestinal cancer in whom there was no evidence of hepatic metastases the Bromsulphalein test was abnormal and in six others without hepatic metastases the Bromsulphalein test was normal. In our experience at the University of Minnesota, the alkaline phosphatase was found to be abnormal in 20 per cent of patients with liver metastases. Thus an increased alkaline phosphatase in patients with no bone disease and no other liver disease might be presumptive evidence of liver tumor. A normal level does not rule out the presence of a liver tumor.

Serum Glutamic Oxalacetic Transaminase Activity as a Means of Determining Hepatic Metastases.—Molander,[43] formerly of the University of Minne-

sota, utilizing a test developed by Karmen[25] has demonstrated, on the basis of animal experimentation, that an increase of the serum transaminase level is indicative of cellular necrosis. In the absence of heart disease this can be diagnostic of liver cell destruction. Utilizing the same test, Wroblewski and LaDue[66] have found the transaminase level to be abnormal in most patients with hepatic metastases. Unless the tumor produces destruction to the hepatic cells, transaminase levels will not be abnormal. In several patients with known hepatic metastasis from breast cancer, the serum transaminase levels were found to be normal.

Cholinesterase.—Molander[42] has indicated that the serum cholinesterase is abnormally low in some patients with hepatic metastases. There is nothing specific about this abnormality and it is but another in the large number of function tests.

We have observed it to be increased following x-ray therapy to the liver. As the serum cholinesterase level is roughly correlated with serum albumin production, an increase in the level suggests serum albumin synthesis. The cholinesterase is usually high in nephrotics because of rapid albumin regeneration to replace that lost in the urine. We have used this level as a rough guide for x-ray therapy. It usually increases during and after therapy, but when it decreases significantly this is interpreted as evidence of hepatic dysfunction, and therapy is terminated.

Other Diagnostic Techniques.—Another technique described to diagnose hepatic tumors includes the selective concentration of radioactive serum albumin by the tumor. Since we have found this test cumbersome and unreliable, we do not use it anymore.

We accordingly conclude that although the various tests may be abnormal in the presence of hepatic tumors, nevertheless similar abnormal values can be produced by nonspecific liver damage. These tests are accordingly nonconclusive to determine the presence of cancer to the liver. In fact, if a patient develops an enlarged liver, with or without jaundice, at a variable period after resection of a primary malignant tumor, an abnormal liver profile is interpreted as presumptive evidence that the disorder is due to primary liver disease (infectious hepatitis, and so forth). To the contrary, a normal liver profile is considered more ominous as being suggestive of the presence of metastases.

Biopsy is the only absolute means of establishing the diagnosis and determining the type of tumor. We routinely use the aspiration biopsy technique of the liver and in the presence of normal blood clotting mechanism have found no abnormalities to occur from its use in a large number of patients. In the majority of instances where it has been used, aspiration biopsy determines not only the presence of a tumor but often the type of tumor present. If a liver tumor is first noted at the time of laparotomy, a formal biopsy is always indicated before a declaration is made that the liver contains cancer metastases. We have seen instances where a harmless, benign tumor of

the liver, either an hemangioma or a nodular hyperplasia, was diagnosed as metastases on clinical evidence. A formal biopsy can be performed with safety.

THE TECHNIQUES OF TREATING LIVER CANCER

The criteria for therapy will revolve about several factors: (1) the general condition of the patient and his metabolic status especially pertaining to liver function; (2) the degree of involvement of the liver, whether one lobe or more than one lobe of the liver is involved by the cancer; (3) the histogenesis of the tumor; (4) the presence of distant metastases.

Factors which influence the therapeutic approach of cancer metastatic to the liver are: (1) The ability to control the primary tumor. (2) The time of appearance of the metastases, before, during, or after the diagnosis and treatment of the primary tumor. (3) The gross characteristics of the growth, whether nodules (solitary or multiple) or diffuse infiltration. (4) The extent of the involvement, whether one or more lobes. Metastases seldom break through the liver capsule and extend to contiguous structures. (5) The route by which the metastases reached the liver; extension by direct growth (gallbladder cancer) could be treated differently from a tumor emboli, which has arrived by the circulatory system. (6) The biologic effect of the metastasis. Certain metastatic growths in the liver may occupy large segments of the liver without appreciably damaging the remainder of the hepatic structure or function (carcinoid tumor) while others will have a profound effect adversely affecting the liver. (7) The blood supply to the metastasis. Most tumors of the liver receive their circulation entirely from the hepatic artery as shown by Mann. Wakim, and Baggenstoss.[34] Chemotherapeutic agents should be given intra-arterially and not ingested or given intravenously. (8) The metabolic condition of the patient. Ascites usually is a most ominous sign. Prolonged severe jaundice will influence therapy. (9) The condition of the remainder of the liver. Radical operations are not indicated for cancer superimposed upon cirrhosis.

The Treatment of Liver Tumors by Irradiation.—Most radiologists have in the past been fearful of administering radiation to patients bearing liver tumors, because of a concept that the liver is unduly sensitive to the effects of irradiation. This concept is unfounded. Observations on the histopathologic changes in the liver following irradiation have been made by numerous workers on various experimental animals with conflicting reports. Warren and Whipple[62] have reported an absence of histologic changes in the liver following deep roentgen therapy. Pohle and Bunting[50] have described an alteration as manifested by initial swelling of the hepatic cells with subsequent atrophy following recovery. Case and Warthin[12] have described three human patients in whom there was extensive damage to the liver following intensive irradiation for cancer. Doub, Bolliger, and Hartman[15a] have observed a loss of about 50 per cent of weight of the liver following fractionated irradiation to dogs. Extensive fatty infiltration and regions of focal necrosis with some increase of fibrous tissue at the peripheral lobule occurred. Rapid regeneration was noted. In view of these conflicting reports, I have studied

Fig. 1.

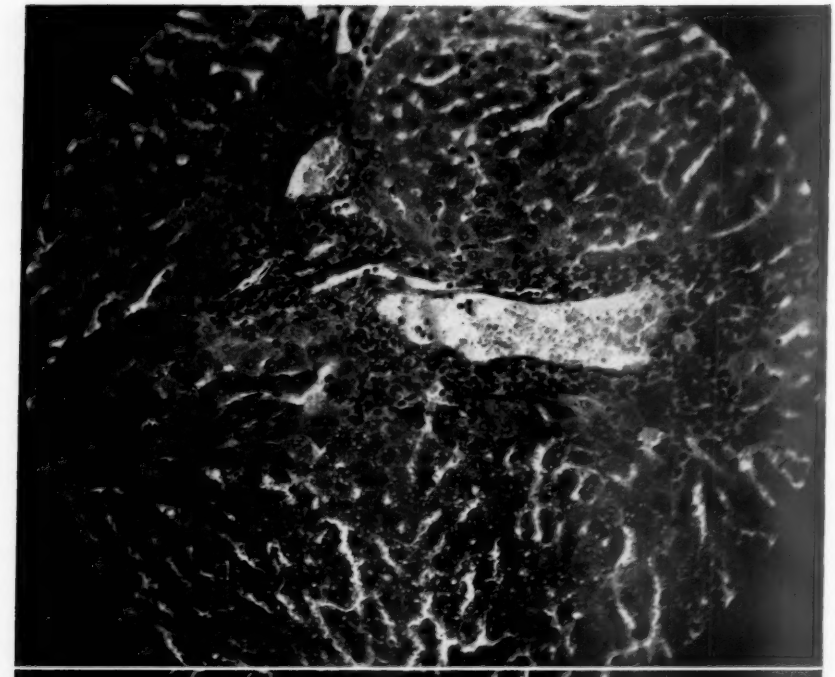


Fig. 2.

Figs. 1 and 2.—Rabbit liver. Twelve hours after 3,000 r., showing inflammation and edema.

(Figs. 1 through 5 published through the courtesy of Radiology, 57: 561, 1951.)

the effects of irradiation upon the liver giving a single massive dose of roentgen radiation to the liver of rabbits in an attempt to enhance and intensify the radiation effects. Briefly, the observations subsequent to therapy consisted of edema, hyperemia, and leukocytic infiltration probably a manifestation of damage to the vascular system. The liver cells were damaged or destroyed in proportion to the dosages, very high doses causing complete necrosis while the lower doses produce only slight evidence of damage. An interesting observation was the focal destruction of the liver demonstrating a variable sensitivity of the liver cells to irradiation. It was my belief, substantiated by glycogen and fat staining, that the hepatic cells which are well nourished and contain abundant glycogen were the least susceptible to dam-

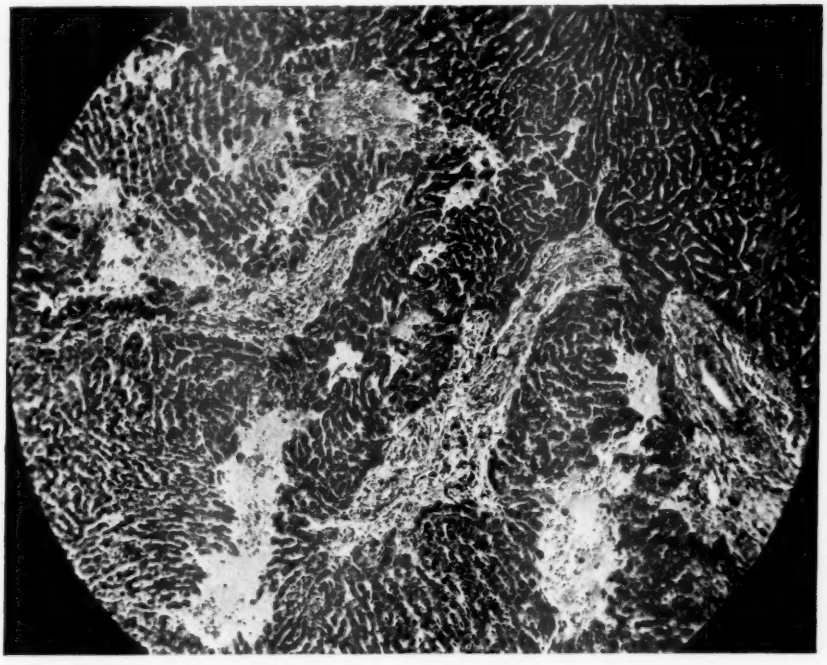


Fig. 3.—Rabbit liver. Two days after 30,000 r., showing patchy necrosis.

age by irradiation. Repair was rapid if the damage was not too extensive. Regions of cellular debris were absorbed, and regenerated hepatic cells filled the defect rather rapidly. There was a minimum of fibroses. Unpublished data has demonstrated that there is an increase of cellular water following irradiation. These observations have encouraged us to study the effects of radiation therapy on a group of patients bearing inoperable hepatic cancer, which results shall be presented.

Chemotherapy of Liver Tumors.—There is no chemical agent which can cure cancer today. The presence of metastatic foci in the liver does not militate against the utilization of chemotherapeutic agents if adequate ones are developed to treat these metastases located in the liver. Although the liver is sensitive to cytotoxic agents, it is the liver's function to detoxify these agents,

Fig. 4.

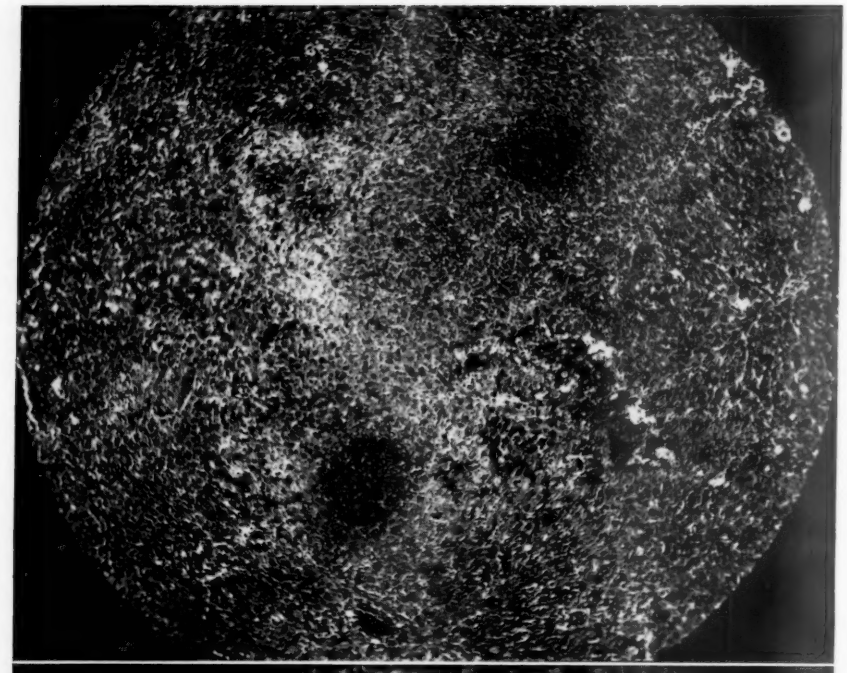
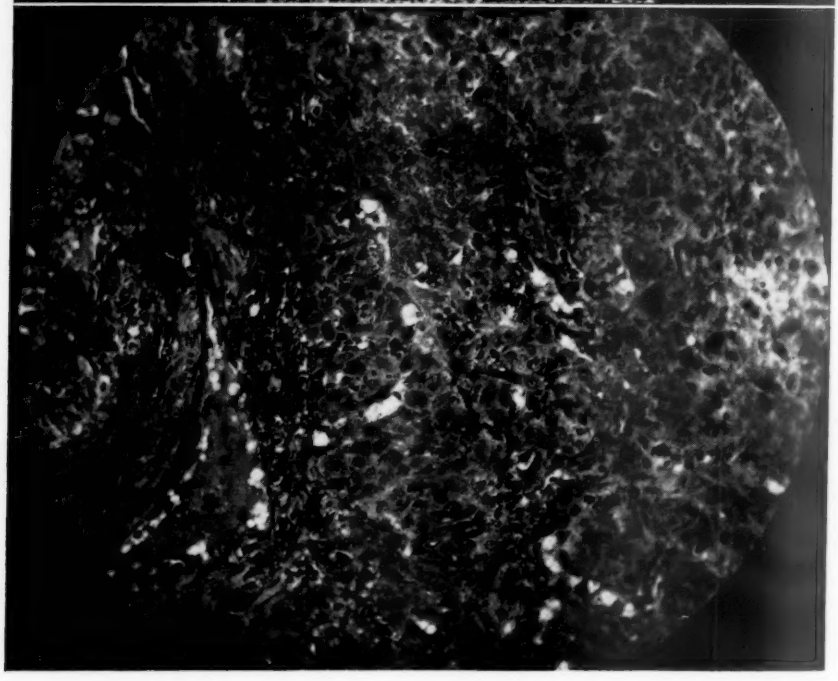


Fig. 5.



Figs. 4 and 5.—Rabbit liver. Three days after 30,000 r., showing coalescing necrotic areas.

and should the remainder of the liver be healthy it can survive the administration of rather large doses of toxic agents in efforts to treat tumors of this organ.

Since most of the liver tumors obtain their blood supply from the hepatic artery, it becomes essential to administer a chemotherapeutic agent by way of the arterial system if a great concentration of this agent in the tumor is to be obtained. The fact that ingested material is carried by way of portal circulation to the liver demonstrates that this would be an unsuitable means of administering chemotherapeutic agents for hepatic tumors. Kremen,[25] from the Department of Surgery of the University of Minnesota, has demonstrated that the intra-arterial administration of large doses of nitrogen mustard (methyl-bis) could be tolerated quite well by dogs' livers. In view of this observation and because personal experience has demonstrated that patients could tolerate large doses of nitrogen mustard, we have explored the possibility of administering this cytotoxic agent by means of a polyethylene catheter introduced either directly into the hepatic artery or threaded through the femoral artery through the aorta to the celiac plexus. The details of these experiments will be presented.

Isotope Therapy of Hepatic Tumors.—Because livers enlarged with lymphomatous infiltrates would shrink following the administration of radioactive phosphorus, we have studied the effects of isotopes upon liver tumors. Radioactive iodine will reduce the size of thyroid metastases in the liver indicating that the nature of the tumor rather than its site is a determining factor in influencing the response to radioactive isotopic therapy.

We have studied the results of intravenous radioactive chromic phosphate to note the effects of a colloidal suspension upon the liver tumors but preliminary evidence has been disappointing and radiohistographs have indicated that most of the colloid containing isotopes would be picked up by the reticuloendothelial system which would surround the tumor, and very little, if any, would penetrate the tumor mass. We have accordingly discontinued this form of therapy for space-occupying masses in the liver but continue exploring its use for lymphomas of the liver. Since relatively small amounts of this radioactive colloid goes to the bone marrow, its use is not accompanied by the severe hematopoietic depression which occurs with crystalloid P^{32}.

We are investigating the effects of various combinations of treatment methods upon inoperable liver tumors as follows: (1) external x-ray therapy, (2) intra-arterial nitrogen mustard alone, (3) intra-arterial nitrogen mustard followed by x-ray therapy, (4) intra-arterial nitrogen mustard followed by intra-arterial P^{32}, (5) intra-arterial nitrogen mustard plus intra-arterial P^{32} followed by deep x-ray therapy, (6) surgical excision.

The Treatment of Inoperable Liver Tumors by Means of Irradiation and Chemotherapeutic Agents.—Fifty patients with liver cancer who received either radiation therapy, intra-arterial chemotherapy, isotope therapy or a combination of these agents, form the basis of this review. The data will be presented according to the therapeutic modalities used

The x-ray therapy given in each instance was medium voltage x-radiation ranging from 200 to 250 kv., HVL 2 mm. Cu, 70 cm. target-skin distance, D/n 2,000 to 4,000 r. Between 250 and 300 r. were given daily to each of four ports for a period which varied from three to five weeks. We have had no experience with the use of rotation therapy for hepatic tumors. The patients tolerated the treatment well for the most part with no untoward results and no excessive radiation sickness. Because of the selective action of radiation upon certain liver cells as described previously (liver cells containing glycogen are apparently more resistant to damage from the x-rays), it was attempted in each instance to give these patients as large a quantity of food as could be tolerated during their therapeutic regime. This is considered to be of the greatest importance. The patient should receive at least from 2,500 to 3,500 calories consisting of a minimum of 100 Gm. of protein, 400 Gm. of carbohydrates, and from 100 to 150 Gm. of fat, supplemented with various dietary supplements. We have routinely used a lipotropic supplement supplied by the U. S. Vitamin Corporation, Methyscol, which contains methionine, choline, inositol, and vitamin B_{12} liver extract. It is taken by mouth during the

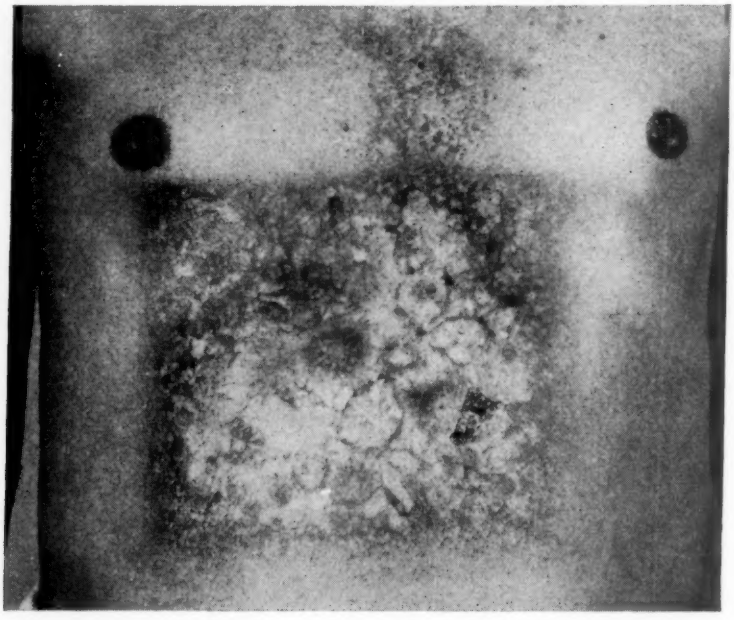


Fig. 6.—Skin reaction ten days after 5,100 r. delivered to liver.

course of roentgen therapy. Where oral intake cannot be tolerated, it is given intravenously or intramuscularly. We have obtained a direct impression that it enhances the tolerance of the patient to radiation therapy. In addition, patients receive adequate quantities of vitamins usually in the form of crude Brewer's yeast, about 50 Gm. per day. Vitamin K is given in doses of 10 mg. per day if any bleeding tendencies are present. Hypoproteinemia must be controlled and, if it cannot be corrected by oral intake, human serum albumin is administered intravenously. It is essential to observe liver function tests

during the course of x-ray therapy and any severe increase in the number and degree of abnormal liver tests dictates the cessation of x-ray therapy. Cortisone or one of the cortisone-like drugs also favorably influences the patients receiving x-ray therapy.

Treatment of Liver Cancer by X-ray Therapy Alone.—Twenty patients of this series were subjected to a course of external irradiation as definitive therapy (Table I). These patients are divided up as follows: (1) Patients with primary liver tumors, and (2) patients with metastatic cancer to the liver. One patient, a 55-year-old white man, with a huge hemangioma involving the left lobe of the liver, was treated with x-ray therapy by Dr. Pack. A dramatic diminution of the tumor which almost filled the abdominal cavity occurred, so that it was barely palpable after treatment. He remained well for fifteen years. This case demonstrates that a tumorcidal dose of x-ray can be given to the liver region and be well tolerated by the normal liver.

TABLE I. THE EFFECTS OF X-RAY THERAPY UPON PRIMARY HEPATOMAS

PATIENT AGE SEX	DEGREE OF INVOLVEMENT	DURATION OF LIFE AFTER TREATMENT	REMARKS
		A. PATIENTS WHO ENJOYED A GOOD RESPONSE	
A. W. 30; F	Both lobes	4 years and 8 months	Decrease in size of mass; sense of well-being
P. A. 27; M	Both lobes—very extensive	9 months	Jaundice subsided; appetite improved; sense of well-being; no control of ascites
R. S. 25; F	Right lobe	1 year and 4 months	Marked shrinkage of mass; metastasis to os pubis also responded well
R. G. 48; F	Both lobes	4 years	Marked response—relief of all symptoms; recurrence occurred; additional x-ray therapy given; good response
M. K. 30; F	Right lobe	4 years and 7 months	Mass became smaller and movable; prolonged control of symptoms; died from hematemesis
Average		3.5 years	
		B. PATIENTS WHO HAD NO RESPONSE TO X-RAY THERAPY	
C. W. 35; F	Both lobes	4 months	Patient metabolically impoverished and could not tolerate treatment
A. G. 40; M	Right lobe	2.5 months	No beneficial response
M. R. 41; F	Both lobes	3 months	No response
A. G. 50; M	----------	4 months	Hematemesis
L. G. 14; F	Both lobes	1 year	Marked ascites; uncontrolled
Average		5 months	

In trying to evaluate the effects of x-ray therapy upon primary liver cancer it became apparent that one group of patients bearing the tumors enjoyed a prolonged period of palliation with the therapy whereas another group suffered a rapidly fatal course even though the same form of therapy was given. Of ten patients with primary hepatic cancer, five enjoyed a good symptomatic response; the average duration of life of these five patients was

3.5 years and varied from 1 to 4.8 years. In sharp contrast was an additional group of five patients who were subjected to the same form of therapy but whose average duration of life after treatment was only five months and varied from 2 to 12 months. It would thus seem that the malignant nature of the primary tumor, with its inherent growth capacity and biologic effect, influenced any effort of treating these tumors. The first group, who bore apparently a less malignant form of tumor, had responded well to x-ray therapy with prolonged periods of excellent palliation. In contrast, rapidly growing tumors resisted any effort at therapy and the patients died shortly after therapy was instituted.

TABLE II. RESPONSE OF METASTATIC CANCER TO THE LIVER TO X-RAY THERAPY

PATIENT	DIAGNOSIS	DURATION OF LIFE AFTER TREATMENT	REMARKS
H. B. 50; M	Metastatic leiomyosarcoma from stomach	3 years	X-ray therapy poorly tolerated
H. P. 52; M	Metastasis from cancer of sigmoid; sigmoid removed 3 years previously	7 months	Good initial response with relief of anorexia, weakness and pain; later developed uncontrolled ascites
M. L. 60; M	Metastatic cancer from sigmoid; removed 3 years previously	6 months	Hepatic pain subsided; anorexia persisted
K. N. 60; F	Metastatic cancer from sigmoid and recurrence of sigmoid cancer	1.5 years	Moderate control of symptoms
L. H. 55; M	Cancer of cystic duct infiltrating liver	6 months	Questionable control of symptoms; severe weakness and anorexia persisted
B. S. 56; F	Cancer of gall-bladder; spread to liver	1 month	No improvement
S. N. 69; F	Cancer of gall-bladder; spread to liver	1 month	Mild improvement
S. B. M	Cancer of gall-bladder; spread to liver	1 month	Moderate improvement

Patients with metastatic cancer to the liver responded in a varied manner to the x-ray therapy (Table II). The average duration of life of ten patients bearing metastases in the liver was only seven months and varied from one to two months. In patients who were extremely ill with marked hepatic dysfunction and metabolic impoverishment the therapy was not tolerated at all and had to be stopped shortly after its commencement. In those patients who had a fairly good hepatic reserve, as manifested by a minimum of abnormal hepatic function tests, the therapy was well tolerated, and there was an amelioration of symptoms, a sense of well-being, an improvement of appetite, and a shrinkage in the size of the masses. The duration of comfort was rather short-lived and most of the patients so treated died from their cancers. One patient, an 8-year-old girl, with a neuroblastoma found at the time of an exploratory laparotomy, has tolerated x-ray therapy very well. Her liver profile three weeks after x-ray therapy is normal (Fig. 7). It is anticipated that the results here will be good. Cases have been reported in which neuroblastomas in the liver have been cured by radiation therapy judiciously given.

On the basis of these observations we may make the following suggestions pertaining to the response of hepatic cancer to irradiation: (1) The liver can

tolerate x-ray therapy well providing it is not too badly damaged either by the cancer, nutritional deficiency, or associated diseases, and if the patient is not metabolically impoverished. (2) If the neoplasms in the liver do not occupy too great an area within the liver, then the beam of radiation which would penetrate a limited segment of the liver will be well tolerated by the patient. If the bulk of the liver is subjected to irradiation, it will suffer radiation effects which will be manifested by radiation sickness. Thus, diffuse metastases over the entire liver should not be treated by a radical course of

A.

LIVER PROFILE OF PATIENT THREE WEEKS AFTER X-RAY THERAPY TO LIVER

Hemoglobin—Gm. %	9.3
Per cent	62
R.B.C.—Million per cu. mm.	3.15
W.B.C.—Thousand per cu. mm.	4,200
Urea nitrogen mg. %	14.9
Phosphorus (inorganic) mg. %	5.7
Alkaline phosphatase S.J.R. units	9.9
Bilirubin mg. %	0.2
Cephalin flocculation	Neg.
Cholesterol—total mg. %	162
Cholesterol esters mg. %	98
Thymol turbidity units	5
Total protein Gm. %	6.9
Albumin Gm. %	3.8
Globulin Gm. %	3.1
Cholinesterase pH units	0.96
Transaminase	48

B.

Fig. 7.—Photo of an 8-year-old girl at the completion of deep x-ray therapy to the liver for a neuroblastoma metastatic to the liver. X-ray was given to 3 ports: left anterior abdominal, right anterior abdominal and left posterior abdominal. She received 200 r. daily to each of 3 ports from July 22, 1955 to Aug. 26, 1955, for a total of 2,400 r. ×3, with the following factors: 250 KV., 50 cm. TSD, 1 Cu filtration, the anterior ports measuring 13 by 10 cm. and the posterior port 15 by 35 cm. which ports were diminished in size with continuation of treatments.

radiation therapy. (3) The large quantity of blood circulating through the liver is one of the factors which would make one expect a good response of liver tumors to radiation therapy. It has been repeatedly observed that tissues with a good circulation will respond best to irradiation in contrast to ischemic tissues in which the radiation effect is not good. Efforts in this study to note the effects of radiation upon the liver's function as measured by hepatic profile has not been too rewarding. It may be stated that certain patients, who have a good hematopoietic reserve at the time of therapy, will tolerate the therapy with very little fall in their red cell mass. In contrast, if the patient has a low hemoglobin at the onset of therapy which has been brought to normalcy by repeated transfusions, this would indicate that the patient's ability to fabricate blood is deficient and x-ray treatment will have

TABLE III. THE EFFECTS OF X-RAY THERAPY TO HEPATIC METASTASES UPON LIVER FUNCTION

PATIENT—H. P.* METASTATIC CANCER TO LIVER FROM PRIMARY OF SIGMOID	3 WEEKS AFTER X-RAY THERAPY	5 WEEKS AFTER X-RAY THERAPY	10 WEEKS AFTER X-RAY THERAPY	14 WEEKS AFTER X-RAY THERAPY	20 WEEKS** AFTER X-RAY THERAPY
Hemoglobin—Gm. per cent	10.8	12.7	13.8	12.8	11.2
Per cent	72	85	91	85	75
R.B.C. per cu. mm.	3,640,000	4,300,000	4,560,000	4,190,000	3,810,000
W.B.C. per cu. mm.	6,600	9,600	7,200	6,200	3,650
Urea nitrogen—mg. per cent	11.3	13.1	10.9	13.5	14.7
Phosphorus (inorganic)—mg. per cent	4.2	3.1	3.7	3.4	3.0
Alk. phosphatase—Bodansky units	16.4	23.7	47.0	47.0	54.2
Bilirubin—mg. per cent	0.6	1.1		2.5	3.5
Bromsulphalein					
mg. per cent 15′	53	55	45	57	44
mg. per cent 30′	44	36	36	40	39
mg. per cent 45′	36	30	32	38	Neg.
Cephalin floc.	+ 1	+ 1	Neg.	Neg.	170
Cholesterol—total mg. per cent	160	230	285	242	54
Cholesterol esters—mg. per cent	101	150	175	154	121
Thymol turbidity units	< 5	< 5	6.1	6.4	< 5
Total protein—Gm. per cent	5.7	6.5	5.7	6.4	6.6
Albumin—Gm. per cent	3.0	2.9	2.6	2.6	3.1
Globulin—Gm. per cent	2.7	3.6	3.1	3.8	3.5
Cholinesterase—pH units	0.33	0.49	0.48	0.51	0.41

*The patient received 5,100 r. to one large port 16 × 18 cm. over the right lobe of the liver with the following factors: 250 kv., 30 ma., filter 1.5 Cu., T.S.D. 70 cm.—300 r. being given daily from 12/22/52 to 1/17/53.

**Patient died two months later.

a deleterious effect. (4) Certain patients will have a minimum of radiation sickness whereas others will have profound radiation sickness following moderate doses of x-ray to the liver. This situation prevails for x-ray therapy given anywhere over the body, and it is my impression that radiation therapy over the liver offers no special problems beyond radiation therapy given elsewhere over parenchymous organs. (5) The liver cells which are starved will suffer greater effects from radiation therapy and therefore every effort must be made to maintain a good hepatic metabolic state. (6) A peculiarity of liver response to irradiation is the paucity of the fibrous tissue response. Although there is a fibrous tissue reaction which is most marked at the periphery of the liver lobules, the aggressive growth capacities of the normal hepatic cells compete with the fibrous tissue reactions so that the damaged foci con-

sisting of cellular debris are rapidly absorbed with a rapid replacement of this defect by normal hepatic cells. This might be construed as being one of the detriments of the response of the liver as a tumor bed to radiation therapy. It has been well demonstrated that the fibrotic response is an important feature in helping to control certain cancers. (7) The histologic form of tumor markedly influences the degree of responses. Thus hemangiomas and neuroblastomas as well as the various lymphomatous infiltrations (Hodgkin's disease, leukemia, reticulum-cell sarcoma, lymphosarcoma, and so forth), will respond very well to x-ray therapy. Tumors from the cervix, bronchial carcinoma, and so forth, will respond fairly well. Adenocarcinomas react most poorly, and thus cancer metastatic from the stomach, rectum, pancreas, and breast do not manifest too great a response. Phillips and associates[48a] used the million-volt x-ray generator to treat hepatic cancer, giving 300 r. to opposing anterior and posterior ports, and delivered a tumor dose of 2,000 to 3,750 r. They observed improvement in 72 per cent of their patients but the duration of life following therapy was short: for metastatic breast cancer in the liver, 1.6 months; bronchogenic cancer, 2.7 months; and cancer of the gastrointestinal tract, 1.2 months.

The Effect of Intra-Arterial Chemotherapeutic Agents on the Treatment of Liver Tumors.—In view of the observations that chemotherapeutic agents such as nitrogen mustard will beneficially influence the course of the patient bearing certain inoperable cancers (bronchogenic carcinoma, lymphomas, and so forth) an effort was made to study the effects upon selectively concentrating large doses of this agent by means of cannulizing the femoral artery, threading an intra-arterial polyethylene catheter through the aorta to the level of the celiac axis and giving the patient a course of nitrogen mustard. (Table IV.) An average of 10 mg. of nitrogen mustard was given per day for a total dose of 50 to 60 mg. It was found that extending beyond this range would not materially influence the progress of the cancer but would result in greater untoward effects from the patient. Accordingly an average of 50 mg. was chosen, regardless of the patient's weight and determined entirely upon the patient's ability to withstand this form of therapy. In each instance the patient tolerated the 50 mg. of nitrogen mustard well. In addition it had been observed that the concomitant administration of an antibiotic appeared to exert a synergistic effect upon the effects of the nitrogen mustard. Accordingly in each instance a total dose of 5 to 8 Gm. of Terramycin was given concomitantly intra-arterially with the nitrogen mustard. The Terramycin was given to these patients also because of the observation that the livers of dogs contain anaerobic bacteria and it was feared that possible destructive effects of the cytotoxic agent upon the liver might activate in some way these intrahepatic organisms and that the concomitant administration of the antibiotic would exert an antiseptic effect. Its administration produced pain.

Fourteen patients bearing metastatic cancer to the liver were treated by the intra-arterial nitrogen mustard regime. The average duration of life of these 14 patients subsequent to the course of therapy was only five months. Although the total effect upon longevity was not significant, certain of the

patients did enjoy rather marked symptomatic palliation. Thus, one patient, S. O., a 59-year-old woman, who had suffered from diffuse metastases to the liver from a papillary cystadenocarcinoma of the ovary which had previously been removed by a radical hysterectomy, was given a course of intra-arterial nitrogen mustard. There was a marked shrinkage in the size of the liver, as well as a complete disappearance of a metastatic lymph node in the supraclavicular region. There was an excellent symptomatic response, a gain of 10 pounds in weight, and the patient became completely asymptomatic. However, the asymptomatic state lasted only three months, after which there was

TABLE IV. THE EFFECTS OF INTRA-ARTERIAL NITROGEN MUSTARD UPON LIVER CANCER

PATIENT AGE SEX	DIAGNOSIS	DURATION OF LIFE	REMARKS
S. A. 64; M	Inoperable cancer rectum; palliative colostomy	2 months	No improvement
L. M. 50; F	Cancer of ovary; metastatic to liver	7 months	Shrinkage of mass; sense of well-being
S. O. 59; F	Papillary cystadenoma; cancer of ovary status post radical hysterectomy; metastatic to liver and left supraclavicular lymph nodes	1 year	Marked shrinkage of liver and lymph node in neck; excellent response; 10 pounds weight gain; patient asymptomatic; lasting 3 months; return of symptoms
S. W. 52; M	Cancer of sigmoid; metastasis to liver	1 month	Marked ascites; no relief
S. T. 41; M	Cancer hepatic flexure; removed 3 months prior; metastasis to liver	7 months	Excellent response; symptomatic; no change in size of mass; patient could eat; felt better; duration 3 months; recurrence of symptoms and another course of treatment given; patient free of symptoms but abdomen remained solid
I. S. 40; M	Cancer of rectum; removed 1½ years ago; metastasis to liver	4 months	No relief
J. K. 45; F	Cancer of rectum; inoperable; hepatic metastasis	6 months	Shrinkage of liver
A. P. 60; F	Cancer of breast; radical mastectomy 4 years before	9 months	Asymptomatic for 5 months after treatment; patient had osseous metastasis
F. W. 61; F	Cancer of uterus; metastasis to liver and abdomen	1 month	No response
E. H. 55; F	Cancer of ovary; metastasis to liver	5 months	Excellent relief of symptoms for 3 months; ascites controlled
F. B. 76; F	Metastatic cancer to liver; 1° not known	4 months	Excellent result; transient relief of pain
J. D. 70; M	Cancer of sigmoid; metastasis to abdomen and liver	1 month	No relief
A. S. M	Cancer of rectum, metastasis to liver 4 years later	3 months	Questionable response
M. S. 64; M	Cancer of cecum; colectomy; metastasis to liver and rectum 18 months later	6 months	Slight improvement of symptoms

a return of symptoms consisting of anorexia and increase in size of the tumor. The patient was accordingly given a course of deep x-ray therapy which had a questionable effect, and she died one year after the course of nitrogen mustard therapy.

In four patients in this group with cancer metastatic from the large bowel, a minimal effect was manifested from this regime. On the basis of

these observations we have formulated the following criteria for treating hepatic cancer with intra-arterially administered chemotherapeutic agents: (1) Extensive hepatic tumors replacing much of the liver usually respond poorly and should not be treated. (2) Patients with marked hepatic abnormalities and who are metabolically impoverished should not be treated by this regime. (3) In the presence of ascites the results are usually poor. In only one instance of this series was a beneficial effect upon the reduction of ascites observed. (4) Patients who have presented prolonged periods of obstructive phenomena in the liver with severe jaundice and other evidence of obstruction respond poorly to this form of therapy. (5) Patients with certain histologic forms of tumors respond better than others. The best response was obtained in patients with ovarian carcinoma and next, patients with uterine carcinoma. Patients with primary lymphoma respond very well to this form of therapy. Patients with metastases from cancer of the gastrointestinal tract respond poorly.

A uniform observation in each of these patients who respond well was the fact that the response was transient in nature and in each instance if the patient did enjoy palliation he did so for a short period, an average of two to three months. There then appeared to be an escape from the chemotherapeutic effect and the tumor again began to grow rapidly and clinical symptoms reappeared. An observation which cannot be explained is the fact that in two patients, after therapy, there was no effect upon the size of the tumor, the abdomen was almost completely filled with a huge liver containing metastases but there was a moderate relief of all symptoms and a sense of well-being.

In view of the observation that the effects from the chemotherapeutic agent were transient in all instances, a program was instituted to give a course of intra-arterial nitrogen mustard and to supplement this chemotherapeutic regime with irradiation.

The Effects of Intra-arterial Nitrogen Mustard Supplemented With Radioactive Phosphorus.—Eleven patients bearing metastatic cancer to the liver were treated by this regime (Table V). It is difficult, if not impossible, to evaluate what beneficial effect the radioactive phosphorus had in supplementing the benefits derived from the intra-arterial nitrogen mustard. The average duration of life of these eleven patients was only six months after the completion of the therapy. We were prompted to use radioactive phosphorus in these investigatiosn because, in a previous study dealing with the effects of intra-arterial nitrogen mustard upon pulmonary cancer, we observed uniformly a very large pickup of P^{32} by the liver. The course of therapy was tolerated well by each patient if the patient had a good hematopoietic system at the onset of therapy. In contrast, if the patient manifested defective hemaopoieses as evidenced by anemia and leukopenia, then a combination of these two severe cytotoxins (the nitrogen mustard and the radioactive phosphorus) would cause the bottom to drop out of the hematopoietic system and a profound anemia and leukopenia would develop which would be very difficult to control. This occurred in one of our patients who had a leiomyosarcoma metastatic from the uterus to the liver and she was discharged with a good symptomatic improvement even to the relenting of the intestinal ob-

struction. However, about ten days after the completion of the therapy she developed a marked anemia and leukopenia. Pneumonia then developed and the patient died.

The usual dose of radioactive phosphorus given was 10 mc. administered at the completion of the chemotherapeutic regime either in one dose or in fractionated doses.

Intra-arterial Nitrogen Mustard Followed by Deep X-ray Therapy.—The next program utilized for the treatmen of hepatic metastases was a combination of intra-arterial nitrogen mustard followed by externally administered x-ray therapy. One such patient, a 63-year-old man, who had metastasis from a sigmoid carcinoma to the liver, received no benefits from the intra-arterial nitrogen mustard and the liver increased in size. When deep x-ray therapy was delivered over two ports measuring 19 by 18 and 12 by 13 cm. with 300 r. given daily alternating to each port for a total of 3,000 r. × 2, an excellent initial response occurred. The liver became smaller and the patient's appetite improved, but he complained of a burning sensation in the region of the liver. One month later he developed ascites, and he died seven months later. Another patient with metastatic cancer of the cecum for which a right colectomy had been performed had a period of remission of all symptoms which lasted six months. This patient died one year after the completion of the therapeutic regime. Two additional patients had a moderate response. One could not tolerate the therapy and it had to be stopped and the other did tolerate it but enjoyed no benefit and succumbed six months after therapy.

Combined Treatment With Intra-arterial Nitrogen Mustard, P^{32}, and Deep X-ray Therapy.—A combined treatment consisting of intra-arterial nitrogen mustard plus radioactive phosphorus plus deep x-ray therapy was given to four patients. Those patients whose livers are not damaged extensively by the tumor can tolerate a combined course of chemotherapy, radioactive isotopes, and x-ray therapy. One such patient who received this regime was a 54-year-old woman who had a cancer of the sigmoid colon resected four years previously. The presence of hepatic metastases resulted in a huge, bulky mass, which produced the symptoms of pressure in the epigastrium, marked anorexia with rapid fatiguability. An exploratory laparotomy was performed with the hope of resecting the large metastases in the right lobe, at which time metastases were observed in both lobes of the liver. Accordingly an intra-arterial catheter was inserted in the left femoral artery and delivered to the celiac axis. This patient was given a course of 50 mg. nitrogen mustard, followed by 10 μc. of P^{32}. She tolerated the course of therapy quite well with limited anemia which was controlled with two transfusions. She then received a course of deep x-ray therapy over the hepatic metastasis. She tolerated this therapy quite well, and although there was no shrinkage in the size of the mass she felt well for a period of six months following the initial treatment with the nitrogen mustard but died ten months later from the liver failure.

TABLE V. THE EFFECTS OF NITROGEN MUSTARD AND RADIOACTIVE PHOSPHORUS UPON LIVER CANCER

PATIENT AGE SEX	DIAGNOSIS	DURATION OF LIFE	REMARKS
S. K. 60; F	Leiomyosarcoma of uterus; treatment by operation and x-ray therapy; metastasis to liver 9 months later		No significant change in size of liver; patient remains well 6 months later
J. B. F	Cancer of breast; metastasis to liver	10 months	Moderate relief for 6 months
E. S. 62; F	Cancer of breast; mastectomy; metastasis to liver 6 months later	3 months	Liver was too badly damaged; patient became stuporous from amytal
T. W. 52; M	Metastatic cancer from stomach extenuous to both lobes of liver	3 months	Good transient relief of symptoms; jaundic improved
A. S.	Cancer of ovary; recurrent; metastasis to liver 2 months	4 months	Marked softening of abdomen; intestinal obstruction relented; severe drop in blood count; toxic hepatitis
L. P.	Cancer of pancreas; spread to liver	10 months	Good initial symptomatic response; marked anemia
R. G. 46; M	Metastatic melanoma to liver	1 week	CVA; question of metastasis
M. C. R. 66; F	Metastatic cancer to liver; previously in sigmoid; metachronous	------	Mild transient relief; lost to follow-up
L. A. 55; F	Cancer of colon; resected 4 years ago; metastasis to liver	8 months	Temporary decrease in size of liver nodules—7 months; rapid recurrence
T. R. 55; M	Cancer of sigmoid; resected metastasis to liver noted at time of resection		Liver swollen; complains of weakness; O.K. 6 months later
H. R. 42; F	Recurrent cell cancer of liver	5 months	Remarkable temporary symptomatic response; liver swollen; slight control of ascites

Summation of the Combined Chemotherapy and Radiation Therapy for Hepatic Cancer.—It is difficult to evaluate from the data on hand the exact role of these agents in influencing the course of the patients bearing hepatic cancer. The series is too small for any definite statement. However, the fact that each of the patients in this series has died subsequent to the course of therapy conclusively indicates that it is not satisfactory for effecting a cure. Many of these patients had metastases elsewhere to their bodies; therefore we are treating one part of the generalized disease and again it becomes difficult to evaluate the effects. Although the effects upon longevity in most of these patients are difficult to evaluate, 50 per cent of them enjoyed palliation. This offers a hopeful sign to continue investigating the effects of combined treatment upon hepatic cancer. We are further stimulated to treat those patients who have limited cancers within their liver and not wait until these cancers become disseminated before instituting therapy. Accordingly, for these patients who have metastases in the liver, discovered at the time of exploration, it is recommended that the primary cancer be surgically resected where possible, an intra-arterial catheter be inserted into the femoral artery and delivered to the celiac axis. A course of nitrogen mustard should then be given followed by deep x-ray therapy if the patient's metabolic status

will withstand this therapy. Further investigation of the effects of radioactive isotope therapy is necessary before it can be recommended as a routine measure. We are gaining experience both in learning about the natural history of hepatic cancers, primary and metastatic, and in developing techniques of applying chemotherapeutic and radiologic measures in dealing with them. If a better chemotherapeutic agent becomes available, we will have the know-how for administering it.

THE SURGICAL TREATMENT OF TUMORS OF THE LIVER

Although the abdominal cavity was the first visceral compartment to be surgically explored, the liver has been the last organ to succumb to subtotal resection. A segment of the liver was removed by Lius in 1886. In 1899, Keen reported a total left hepatic lobectomy for cancer, but a lapse of about twenty-five years occurred before left lobectomy was again performed.

Wangensteen[61] reported that on Nov. 30, 1949, he successfully removed the entire right lobe of the liver. He described the control of bleeding "by the application of Blalock clamps to the hepatic artery, superior mesentery artery, and portal vein during the excision, plus ligation of the hepatic vein after clamping as they were encountered." Raffucci[52] has indicated that a fifteen-minute span is the maximum that ischemic pressure can be applied safely to the hepatoduodenal ligament. Clatworthy,[12a] a former resident of Wangensteen's, performed a total right hepatolobectomy for a hepatoma in a 17-month-old infant in March, 1952. He used the dissection technique for the resection. The patient died two and one-half months later. Lortat-Jacob and Robert[31] in 1952 effected a successful right hepatic lobectomy for metastatic cancer. Mersheimer[38] performed a total right hepatolobectomy in a male for primary cancer. The patient died fourteen months later of recurrence. Quattlebaum,[51] in January, 1952 performed a successful right lobectomy for a primary cancer of the liver. His patient was asymptomatic for eighteen months, but died twenty-two months after operation from a recurrence.

Pack in 1953 was the first to resect successfully the right lobe of the liver for a primary malignant tumor whose patient survived for a prolonged period (three years). He was also the first to perform a successful right hepatolobectomy for primary cancer of the gall bladder which had spread to the liver. This patient is still living one and one-half years after the right hepatolobectomy.

As increased numbers of liver resections are being performed, an evaluation of their accomplishment will be permitted.

Prognosis Following Resection of Hepatic Neoplasm.—It is impossible at this date to present a statistical report of cures being obtained following the surgical resection of hepatic cancer. The routine performance of hepatic lobectomy is a relatively recent procedure and sufficient data have not been accumulated to adjudge its accomplishments.

Partial hepatic resections have been performed by the surgical department of the Pack Medical Group for various neoplasms: (1) Two massive hemangiomas have been successfully excised, one in a woman who was six months' pregnant, and whose hemangioma grew rapidly under the influence of the pregnancy. (2) A differentiated hepatoma was excised by segmental excision from the right lobe of the liver ten years ago. (3) A right hepatic lobectomy for metastasis from a primary cancer of the sigmoid which had been resected fifteen days previously. This patient remains asymptomatic almost one year later. (4) A left hepatic lobectomy for a metastatic cancer, the primary remaining undiscovered. The patient enjoyed palliation for one year, at which time she succumbed. (5) Sigmoidectomy with primary anastomoses and left hepatolobectomy in one stage for colonic cancer, metastatic to the liver. (6 Segmental resection of the right lobe for a metachronous metastases from an ocular melanoma, which had been resected 14 years previously. The patient enjoyed palliation for two years after which she succumbed from generalized melanoma. (7) A right hepatic lobectomy has recently been performed for cancer of the gall bladder. (8) A right hepatic lobectomy was performed for metastatic spindle-cell sarcoma. (9) Palliative left hepatolobectomy and subtotal right lobectomy for hepatoma. The patient died three years later from generalized metastases.

SUMMARY

The problems pertaining to the treatment of liver cancer have been discussed. The natural history of primary and metastatic cancer to the liver have been presented. Experience gained from treating 50 patients with inoperable hepatic cancer by chemotherapeutic and radiologic methods have been presented.

The surgical attack upon the liver has been discussed.

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SURVIVAL FOR MORE THAN FIVE YEARS AFTER PANCREATODUODENECTOMY FOR CANCERS OF THE AMPULLA AND PANCREATIC HEAD

CLARENCE DENNIS, M.D.,* BROOKLYN, N. Y., AND RICHARD L. VARCO, M.D.,** MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota, The Minneapolis General Hospital, and the Department of Surgery, State University of New York College of Medicine at New York City, and Kings County Hospital)

SINCE Whipple, Parsons, and Mullins[38] first removed a portion of the duodenum and pancreatic head for carcinoma of the ampulla of Vater in 1934, and since the first pancreatoduodenectomy for carcinoma of the head of the pancreas by Brunschwig[4] in 1937, radical resection of this area has received the attention of many surgeons.

Initially it had been hoped that such operations would be curative in a fair share of cases, but as time has passed and data have been accumulated, few instances of cure or even of five-year survival have been reported. The tendency, therefore, has developed, as expressed by Cattell and Pyrtek,[8] and by Parsons,[25] to be disturbed about the wisdom of the use of the radical procedure at all except in the case of ampullary lesions.

It is the purpose of the present article to report from our experience three cases of ampullary carcinoma and two cases of carcinoma of the pancreatic head in which the patients have survived five years or more, to call attention to the long-surviving cases that we have been able to find in the literature, to indicate some points which seem of importance to us in the care of these cases, and to add support to that wholesomely more venturesome and hopeful outlook expressed by Brunschwig[6] in his report of cures, and by Orr[22] in his excellent review, with which our experience with the cases reported in this paper leads us to agree.

CASE REPORTS

CASE 1.—E. J., UH #726757 (RLV): carcinoma of ampulla—local resection: This 55-year-old man was first admitted to the University Hospitals on Dec. 11, 1942. He gave a history of having worked with methyl chloride in the course of refrigerator repair work since 1938. He had had recurrent bouts of fever for the two or three months prior to admission, with the temperature spiking at times up to 102° to 103° F. These episodes had become more frequent. His fever had failed to respond to sulfathiazole therapy. In August, 1941, and again in February, 1942, he had had x-ray studies of the gall bladder, and these had in each instance revealed a nonfunctioning viscus. Surgery had been advised, but refused by the patient at these times. Prior to this admission, the first at our hospital, he had developed painless jaundice. The stools had been light and the urine had been dark. There had been some itching of the skin. The bouts of fever had been recurrent and persistent. The one minute serum bilirubin was 3.6 mg. per cent, the total 5.5. The patient was pre-

*Professor and Chairman, Department of Surgery, State University of New York College of Medicine at New York City, Brooklyn, New York; formerly Professor, Department of Surgery, University of Minnesota.

**Professor, Department of Surgery, University of Minnesota, University of Minnesota Hospitals.

pared for surgery by vitamin K and whole blood transfusions. On Jan. 14, 1943, he was operated upon through a right rectus incision. The liver appeared to be involved in a biliary type of cirrhosis of an advanced degree. The gall bladder and common duct were found to be enlarged, thin-walled and without stones. At the ampulla, a freely movable tumor was noted. A duodenotomy was made over the tumor, and a local resection was carried out, removing about 1 cm. of normal duodenal mucosa in all directions around the ampullary lesion, together with the distal ends of the common and pancreatic ducts. This was carried through the full thickness of the duodenum to the adjacent pancreas. The grossly normal resected segment of common duct was 1 cm. in length. Intestinal continuity was restored by an end-to-end anastomosis of the duodenum using catgut and interrupted silk sutures. After approximating the stomas of the divided pancreatic and biliary ducts with catgut in the form of a figure-of-eight, the duodenal mucosa was anastomosed directly to the mucosa of the pancreatic duct and subsequently to the biliary duct. Closure of the abdominal cavity was accomplished with interrupted silk sutures. Sulfathiazole was placed in the wound during closure and a small amount about the anastomosis prior to closure. A No. 16 catheter, with the distal end running down into the reconstructed duodenum, was left in the common duct as a splint to maintain this opening. A similar splint was left in the pancreatic duct. Convalescence from this procedure was straightforward, and the patient left the hospital on Jan. 30, 1943.

Pathologic examination of the tumor removed from the ampulla was that of a gross lesion measuring 4 by 3.5 by 3.5 cm. Microscopic examination of this tumor revealed epithelial cells forming papillary structures which were quite atypical and intensely staining.

The conclusion was papillary carcinoma of the ampulla of Vater; lymph nodes removed for biopsy purposes revealed only hyperplasia; biopsy of the liver was that of obstructive cirrhosis.

The patient had gained 45 pounds in weight and was well until early in 1945 when he developed recurrent bouts of fever associated with anorexia, nausea, pruritis, dark urine, light stools, and jaundice. A serum bilirubin determination indicated a 1 minute value of 1.3 mg. and a total of 1.4. A plain film of the abdomen indicated that the tube in the common duct had not as yet passed. He was admitted and re-explored on March 27, 1945. At this time the gall bladder was found to contain stones, and numerous concretions had developed about the tube splint. After the common duct had been opened, it was possible to take this tube out and pass a finger through the dilated common duct past the site of the reanastomosis of the common duct to the duodenum. There was no evidence of local recurrence of tumor. After excision of the gall bladder, a catheter was placed through the cystic duct into the common duct and through the anastomosis. Convalescence from this operation was uneventful and the patient was discharged on April 7, 1945. The tube in the common duct by way of the cystic duct was removed on Aug. 6, 1945.

In 1947, a rectal polyp was removed endoscopically, and, on Feb. 15, 1952, the abdomen was opened for removal of polyps of the sigmoid colon. General abdominal exploration at this time failed to reveal evidences of recurrence of the ampullary cancer.

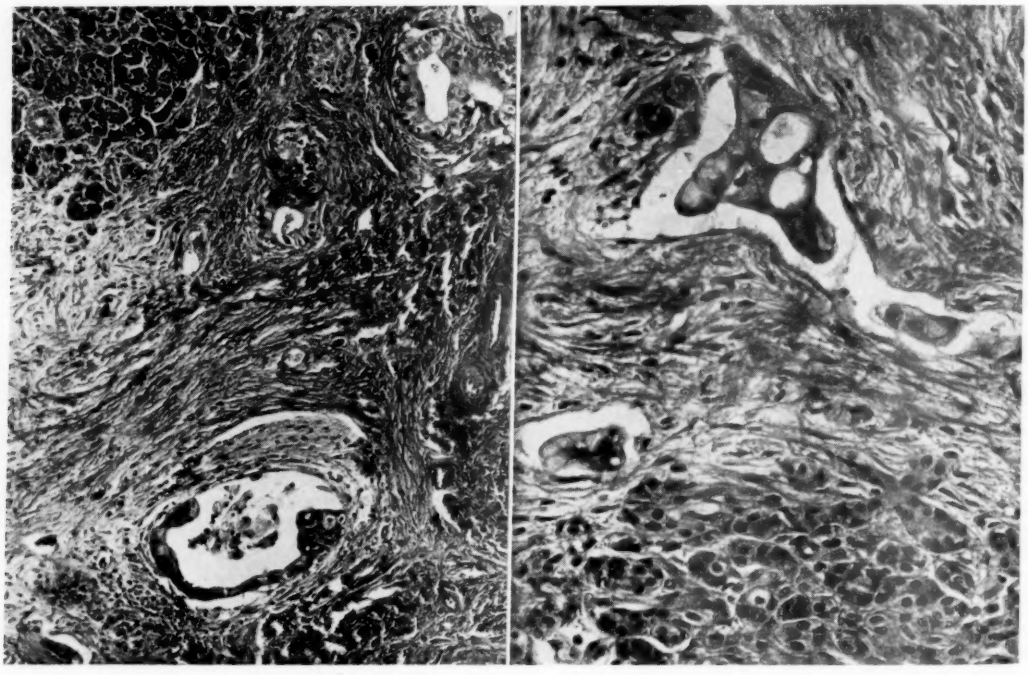
This patient is seemingly free of recurrent malignancy after an interval of almost thirteen years. A cure appears to have been achieved despite the localized type of resection performed. Our subsequent experience, however, leads us to feel that a higher proportion of cures should be anticipated by utilization of radical resection than by local excision for ampullary cancers.

CASE 2.—Mrs. A.S.S., MGH #381-A, 1945 (C. D.): carcinoma of pancreas—radical resection:

This 70-year-old white woman was admitted to the Minneapolis General Hospital on Nov. 13, 1943, complaining of recurrent epigastric pain of eight months' duration, dyspnea on effort, ankle edema, and orthopnea. Her story was otherwise irrelevant. Examination showed her general condition to be good except for a blood pressure of 190/100, cardiac

enlargement, a systolic murmur present over the entire precordium, auricular fibrillation, and a liver 6 cm. below the costal margin. With a diagnosis of arteriosclerotic heart disease with auricular fibrillation and failure, she was treated by rest, digitalization, and supportive measures, and was dismissed, much improved, on Dec. 4, 1943.

She was readmitted late in January, 1945, complaining of dizzines, nausea, and discomfort in the right upper quadrant of 18 days' duration. She had noted dark urine, light stools, vomiting, and a yellow skin for a week as well. She had been taking digitalis regularly. Examination showed a pulse of 92, blood pressure 120/75, deep jaundice, and an enlarged heart with a soft apical systolic murmur. The abdomen was soft, the liver 3 cm. down, and a mass corresponding in position to the gall bladder was palpable. Roentgenograms showed an old tuberculosis of the left lung, a right pleural effusion, and a "negative" gastrointestinal tract. Hemoglobin was 90 per cent; prothrombin time 26.5 seconds compared to a control of 21.5 seconds. Icterus index was 167; cephalin-cholesterol flocculation was 2 plus. The stools showed a 2 plus benzidine test, and 3 mg. of fecal urobilinogen per day.



A. *B.*

Fig. 1.—Photomicrographs of tumor removed in Case 2. (*A*, ×85; *B*, ×300, reduced ⅙.)

On Feb. 9, 1945, with the icterus index now 214, a small right subcostal incision was made under general anesthesia, and a cholecystostomy was performed. At this time, a very hard mass the size of a golf ball was felt in the head of the pancreas. After this procedure, her condition improved greatly, her icterus decreased, and she was able for the first time to gain strength with an appropriate diet.

On March 28, 1945, the patient's condition permitted a radical pancreatoduodenectomy, which was performed under cyclopropane and curare anesthesia, employing a right Perthes incision. The mass in the head of the pancreas was as previously noted, and the pancreas was normally movable. The liver appeared free of metastases. The gall bladder contained several faceted stones, and the site of the cholecystostomy was adherent to the abdominal walls about the cholecystostomy tube.

Radical pancreatoduodenectomy was performed cautiously. The inferior mesenteric vessels and hepatic artery were freed in so far as possible before division of the midportion

of the stomach, the jejunum 8 cm. beyond the ligament of Treitz, and the pancreas 2.5 cm. to the left of the palpable tumor. Vessels were ligated with fine silk as exposed. The entire duodenum was removed, and the common duct amputated 2 cm. above the margin of the duodenum. It became apparent on removal of the specimen that the right and left heptic ducts had not yet joined at the level of amputation. The right duct, which had been drained by the cholecystostomy, contained thick green bile, and the left a milky-white thin fluid. End-to-end closed anastomosis of the hepatic ducts to the jejunum was made, bringing the latter through a rent in the right transverse mesocolon. A No. 14 F catheter was inserted 2 cm. into the main pancreatic duct and secured by a purse-string suture of catgut, the other end being inserted by a puncture wound into the jejunum close to the biliary anastomosis, with pancreatojejunal silk suture serosal approximation. A retrocolic closed Hofmeister-Polya gastric anastomosis was made 45 cm. below the biliary anastomosis. Drains were laid close to the pancreatic and biliary anastomoses, and the wound was closed with 4-0 silk. Cholecystectomy was omitted because of the patient's unstable condition and in fear of contamination of the rest of the field from drainage adjacent to the catheter. The procedure was prolonged to 12 hours, primarily because the precarious cardiac status precluded transfusion in the management of blood pressure depression, which occurred several times. On these occasions the field was covered with moist packs, and a period of 15 to 30 minutes was permitted for recovery.

The pathologist's report was as follows: Specimen consisted of 8 cm. of the distal stomach together with approximately 13 cm. of the duodenum and the head of the pancreas. There was a tumor mass present in the latter region. It was hard and indurated and measured 4 cm. There was approximately 3 cm. of normal-appearing pancreas distal to the tumor. The tumor encroached upon the ampulla of Vater. Sections from the head of the pancreas showed a scirrhous type of carcinoma with nests of poorly differentiated glands (Fig. 1). Sections of the distal end of the pancreas showed no evidence of involvement. The tumor was confined to the region of the head. Sections showed the wall and submucosa of the duodenum in the region of the ampulla of Vater to be invaded by carcinoma in the form of poorly differentiated glands. Sections of the common bile duct showed nothing of note other than scattered lymphocytes.

Conclusion was carcinoma of head of pancreas.

The patient was very ill for several days. There was some drainage from the wound postoperatively, but this finally healed, and she was dismissed May 4, 1945.

The patient returned Sept. 27, 1945, having gained 25 pounds. She complained of bile drainage from the cholecystostomy tube, with discomfort on clamping it. Exploration showed that passage of a stone into the hepatic duct had occurred; it was found impacted at the anastomosis. No evidence of metastases was found. After removal of the impacted stone and cholecystectomy, she recovered easily.

She was readmitted Jan. 23, 1946, for dyspnea, orthopnea, and cough of two weeks' duration. Mild cardiac decompensation was again found, and she improved on medical management.

On Jan. 2, 1950, she was readmitted after a fall on ice in which she had suffered an intracapsular fracture of the left femur and a Colles fracture of the left wrist. The following day a spiking fever developed, and blood cultures showed *B. coli.* Cholangitis was diagnosed and Aureomycin given, with permanent relief. A Smith-Petersen nail was placed in the hip after reduction, and the wrist was immobilized in plaster. Following Dicumarol therapy for phlebitis and pulmonary infarction, she left March 6, able to walk with crutches.

The patient was readmitted four times in 1951, 1952, and 1953 for failure secondary to arteriosclerotic heart disease. On each occasion she responded to the use of digitalis, diuretics, and bed rest.

On May 25, 1954, she entered the Asbury Methodist Hospital for therapy of a compression fracture of the first lumbar vertebra suffered in a fall at home, and complicating recurrent cardiac failure. She was treated by a minimum of bed rest, digitalis, and diuretics, and left the hospital June 7, 1954.

Her final admission was to Asbury Hospital on Nov. 8, 1954. She was treated under a diagnosis of marked cardiac decompensation, complicated by probable pneumonia of the lower right lung. Electrocardiograms showed persistent auricular fibrillation with a fast ventricular rate. The hemoglobin was 72 per cent, the blood urea nitrogen 23 mg. per cent, the bleeding and clotting times were normal, the total protein level was 5.8 Gm. per cent. Serum sodium and potassium levels were normal, but there was occult blood in the stool (guaiac, 2 plus).

She failed to respond to further digitalization, diuretics, and careful medical management. There was persistent edema of the legs, more marked on the right. On November 29 she had "an attack of acute cardiac failure." Respirations doubled, the pulse increased, and she became cyanotic. Although there was some improvement thereafter, she gradually failed, and died on Jan. 5, 1955, 9 years, 11 months after her decompression cholecystostomy, and 9 years, 9½ months after her definitive radical pancreaticoduodenectomy.

Autopsy: The estimated weight was 85 pounds, and the body looked emaciated. There was 1 plus edema of the left leg, 4 plus of the right, extending to the thighs. The abdomen was clean and free of adhesions or evidences of recent inflammation. The liver was 4 cm. below the costal margin. The pleural cavities were both obliterated by dense adhesions. There was hydropericardium (150 c.c.). The pulmonary artery was opened in situ; the left main branch was patent and free of clot. The right branch was found occluded by a large premortem thrombus which had already undergone partial organization. The thrombus filled the entire lumen of the right main pulmonary artery and measured 6 cm. in length. The heart weighed 470 Gm. The coronary arteries were extensively calcified but were widely patent. The right ventricle was normal in size; all other chambers were markedly dilated, and there was apparent insufficiency of the pulmonary, mitral, and tricuspid valves. The right lung showed a large infarct involving the lowest lobe. On section, the area of infarction had a yellow anemic appearance suggesting a duration of several weeks. Edema and congestion were apparent on section of both lungs. A small caseous area was present in the left upper lobe. The liver weighed 1,000 Gm. The left lobe was completely atrophic. The remaining portion of the pancreas weighed 45 Gm. On section, the pancreatic parenchyma appeared to be atrophic; numerous small cysts up to 1 cm. in diameter were scattered throughout it. They contained mucoid material. The intestinal tract was normal except for the changes produced at operation, several small flat polyps in the stomach, and diverticulosis of the left colon. No sign of metastases or recurrence was found.

Microscopic examination showed organizing thrombi in both lungs, "heart disease cells" in the alveoli, areas of bronchopneumonia, and one area of fresh infarction. The right lobe of the liver was involved with mild passive congestion; the left lobe showed marked atrophy of the liver parenchyma. In the pancreas, the parenchyma was largely replaced by fibrosis. The ducts were dilated and the walls infiltrated with mononuclear cells. Few islets of Langerhans were seen, but these were normal in appearance. The acinar tissue was isolated in circumscribed areas by the dense fibrous tissue.

The patient, therefore, survived a few weeks less than ten years following radical pancreatoduodenectomy performed for carcinoma of the head of the pancreas, ultimately to die of unrelated disease. This prolonged survival occurred in spite of the following unfavorable factors: (1) arteriosclerotic heart disease with decompensation before signs of cancer of the pancreas; (2) septuagenarian status; (3) necessity for decompression cholecystostomy alone as the initial procedure because of arteriosclerotic heart disease with decompensation; (4) failure of decompression of left hepatic duct by cholecystostomy, with secondary atrophy of left lobe of liver; and (5) late pancreatic atrophy and fibrosis, presumably secondary to pancreatic obstruction before, and possibly after, operation. In spite of lack of consistent pancreatic substitution therapy, fatty degeneration of the liver was not present at autopsy.

This was the first case performed by the pattern suggested by us in 1946.[14] It seems appropriate to regard this case as a cure, inasmuch as thorough autopsy failed to disclose residual cancer more than nine years after operation.*

CASE 3.—Mrs. C. A., UH #736757 (CD): carcinoma of ampulla—local resection, followed by recurrence and radical resection.

This 58-year-old white woman was first admitted to the University of Minnesota Hospitals on Oct. 12, 1943, complaining of painless jaundice. About six months earlier she had first noted that fatty food tended to be followed by nausea, later by frank vomiting. This had passed after two or three months. About three weeks before admission, painless jaundice had appeared, with dark urine, and light stools. She had lost 21 pounds in six months, weighing 129 pounds on admission.

Examination showed a fairly well-nourished woman with jaundice and skin excoriations, and with a mass about 7 cm. in diameter in the position of the gall bladder. Other findings were not relevant.

Laboratory studies showed normal blood and urine routine studies, serum bilirubin 12.75 mg. per cent at one minute and 18.6 mg. per cent total. Stool studies showed 22 mg. of urobilinogen per day, interpreted as indicating an ampullary lesion or a calculus in the duct.

On Oct. 21, 1943, exploration was done through a right subcostal incision under spinal and cyclopropane anesthesia. A carcinoma of the ampulla was found, without recognized metastases. A local excision was performed, taking as much bile and pancreatic ducts as possible beyond the limits of the tumor. The dilated bile duct was reimplanted higher in the duodenum. The pancreatic duct was not considered dilated, and was therefore ligated without reimplantation. A Penrose drain was placed, leading from the repaired area in the duodenum to the postaxillary line. A mixture of sulfonamides was implanted over the suture line, which was walled from the general peritoneal cavity by omentum. A T tube was placed in the common duct.

The pathologist's report was as follows: The entire specimen measured 3 by 2.5 by 2.5 cm. Three centimeters of common bile duct were present and 3 cm. of pancreatic duct. There was a stricture in the common bile duct extending for a distance of 1.5 cm. above its opening into the duodenum. This stricture admitted a needle about 1.5 mm. in diameter. Above the stricture the duct measured 2.5 cm. in circumference and contained necrotic debris. The pancreatic duct entered the common bile duct at a point 6 mm. above the distal end of the common bile duct. The pancreatic duct likewise admitted a similar-sized needle with difficulty. The proximal portion of the pancreatic duct above the constriction was 7 mm. in diameter. The duodenal mucosa adjacent to the ampulla of Vater was indurated and thickened. Section through the distal end of the ampulla of Vater, including the adjacent mucous membrane of duodenum, revealed dense fibrous tissue in which were embedded well-formed, dark-staining, atypical glands; and there was considerable lymphocytic infiltrate. These carcinomatous glands extended into the duodenal mucosa. Section through the proximal line of resection, including both the common bile duct and pancreatic duct, showed the lining of only one of the two ducts to remain. This was partially necrotic. A few rather deep-set glands were present adjacent to it and also adjacent to another edge of the section which may have represented the deeper portions of one of the ducts. Whether this was pancreatic or common bile duct cannot be stated from the microscopic section. There was no evidence of tumor in this section. Section of the indurated mucosa of the duodenum adjacent to the ampulla of Vater revealed dense fibrous tissue and small cords of epithelial cells replacing both the inner and the outer muscular layer. The mucosa proximally toward the ampulla was ulcerated and replaced by tumor tissue. Distally along the distal line of resection there was a short portion of the wall of the duodenum which was free from tumor. This latter represented the distal line of resection.

*The authors wish to express appreciation to Dr. T. E. Bratrud, who served with one of us (C.D.) at the Minneapolis General Hospital and performed the original exploration and assisted at the resection. They are also grateful to Dr. Charles Neumeister and Dr. Einar Monson for invaluable follow-up data, and to Dr. Frank Ankner for care of the fractures in 1950, and to Dr. S. T. Nerenberg, pathologist at Asbury Hospital, who made his autopsy findings available to us.

Conclusions were carcinoma of the ampulla of Vater and obstruction of the common bile duct and pancreatic duct.

The course postoperatively was smooth until a duodenal fistula developed seven days after the procedure. This was treated by conservative methods in view of the small amount of drainage, and healed in about ten days. The T tube was removed before the patient left the hospital on Nov. 14, 1943.

The patient did nicely without gastrointestinal difficulty until August, 1947, when a bout of diarrhea occured, followed by pale stools and some nausea. She had vomited twice in the week preceding admission on Dec. 5, 1947. Examination showed huge gastric dilation and rather marked dehydration. The serum bilirubin was 2 mg. per cent total. No further special studies were done.

On Dec. 9, 1947, exploration through a transverse incision under Pentothal-curare-nitrous oxide anesthesia revealed a mass the size of an English walnut at the site of the previous tumor. The right ureter was involved in this mass. No evidence of metastases was recognized. A radical pancreatoduodenectomy essentially the same as for case 2 was performed, plus a right nephrectomy. The common hepatic duct was used for anastomosis because of low implantation of the cystic duct, and the gall bladder was removed. The postoperative course was uneventful with the exception of development of a very mild diabetes, which was handled without insulin. She left the hospital Dec. 20, 1947.

The essence of the pathologic report was as follows: Gross—Portion of stomach, duodenum, right kidney, and gall bladder. The main specimen weighed 280 grams. There was a tumor mass surrounding the ampullary region measuring 5 by 4 by 4 cm. The mass was penetrated by two dilated ducts; the proximal duct projected 2 cm. beyond the mass and measured 8 mm. in diameter, and showed distortion and constriction by tumor, particularly a large lymph node projecting into the lumen. It emptied into the duodenum by a pinpoint opening. The more distally situated duct projected 1.5 cm. beyond the tumor and was 1 cm. in diameter. No duodenal opening could be found. In the region of the point at which the proximal duct emptied there was an area of ulceration of the duodenal mucosa. Over its external surface the tumor appeared to be smooth and covered by peritoneum. A 2 cm. segment of ureter was loosely adherent by fibrous adhesions to the tumor posteriorly. The duodenum measured 28 cm. in length, the first portion being dilated, measuring 10 cm. in circumference. Distally it measured 4.5 cm. in circumference. Sections through the tumor showed an adenocarcinoma composed of fairly well-formed glands growing in a dense stroma. It was shown extending beneath the duodenal mucous membrane into the surrounding fat and replacing the structure of the lymph node bulging into one of the ducts. A lymph node from the region of the cystic duct showed hyperplasia. The antral mucosa showed a moderately severe mononuclear infiltrate with some glandular atrophy.

Conclusions were adenocarcinoma of ampulla of Vater (recurrent); metastatic adenocarcinoma of regional lymph nodes; kidney.

The patient was last contacted May 2, 1952, at which time she was doing very nicely, being symptom-free, and doing her daily housework without difficulty. She had gained 20 pounds and was too heavy. She refused to report for examination, insisting she was absolutely well and all she needed was glasses.

This patient was reported, through Dr. T. E. Bratrud, to have died in February, 1954, after a course suggestive of abdominal carcinomatosis. No autopsy was permitted.

CASE 4.—M. E. O., UH #760234 (RLV): carcinoma of ampulla—radical resection.

This patient, aged 56 years was first admitted to the hospital Dec. 3, 1945, and discharged on Dec. 21, 1945. She had been bothered by the first attack of right upper quadrant pain in May, 1945. This had been associated with anorexia, nausea, vomiting, chilly sensations, and, in a few days, evidence of jaundice. Similar bouts had occurred in August and September, 1945. There had been a persistent anorexia between these episodes, in association with which there was a 25 pound weight loss. The usual laboratory tests were within normal limits save for the presence of occult blood in the stool on repeat examinations. A cholecystogram obtained at this time indicated a nonfunctioning gall bladder. After a period of observation, the patient was discharged with a diagnosis of chronic cholecystitis and cholelithiasis.

Since the patient continued to have difficulty, she was readmitted on Jan. 21, 1946. On January 24, through a right subcostal incision, the gall bladder and common duct were found to be distended. Neither contained palpable stones, but in the region of the ampulla there was a very definite mass. Numerous enlarged nodes were present. The impression was that these were probably hyperplastic. A radical pancreatoduodenectomy and partial gastric resection was carried out, removing 20 per cent of the stomach. The head and uncinate process were removed along with the neck of the pancreas to about the level of the mesenteric vessels. The end of the divided jejunum was closed and an end-to-side anastomosis carried out between the divided common duct and the jejunum. Distal to this, an anastomosis was carried out between the pancreatic duct and the jejunum, and finally, about 25 to 30 cm. distal to this, anastomosis was carried out between the stomach and the jejunum, using the Polya pattern. The gall bladder was removed. A catheter was placed in the cystic duct, down through the common duct and through the anastomosis of the common duct to the jejunum. Closure was carried out with silk sutures.

On gross pathologic examination, the mesentery of this area was studded with 26 small lymph nodes. The line of resection of the pancreas was approximately 4 cm. from the tumor. It was impossible to pass a probe into the duodenum from the common duct. Microscopic examination through the tmor mass at the ampulla indicated an abrupt transition to irregular tumor glands, originating in the ampulla and extending through the wall surrounding the common bile duct. There was superficial invasion of the adjacent pancreas.

Conclusions were adenocarcinoma of the ampulla; chronic cholecystitis; negative lymph nodes for tumor metastases.

Convalescence from this procedure was fairly straightforward, being delayed only slightly by an interim of gastric distention and vomiting which responded to a period of nasal siphonage. She was dismissed Feb. 14, 1946. In the period since her operation, the patient has been seen many times in the Outpatient Clinic and continues to do well.

When seen in 1954 by her family physician, x-rays of the colon, chest, and stomach were all normal. No evidence of tumor recurrence could be detected in this examination. Her health was stated to be good. A personal letter from her in 1955 reaffirms this picture of freedom from ill health or suggestions of recurrent malignancy.

Case 5.—J. M. H., UH #801951 (C. D.): carcinoma of pancreas—radical resection.

This 70-year-old white man was admitted on March 18, 1949, and discharged on April 20. At the time of this admission, patient had jaundice associated with generalized pruritus, and in addition, he had noticed the passage of dark urine and light-colored stools. These phenomena first appeared about six weeks prior to this date, and during this interval there had been an associated 10 pound weight loss. A soft, round, palpable mass was present in the right upper quadrant. Pertinent laboratory studies were a stool examination, 4 plus to guaiac, and a gastrointestinal series with barium showing a deformity of the second portion of the duodenum. The one-minute serum bilirubin was 1.2 and the total was 18 mg. per cent. The quantitative feces urobilinogen was 3 mg. per day. The patient was prepared for surgery using streptomycin and sulfasuxidine by mouth. Vitamin K was also given in the course of this three-day preparation.

On March 25, the patient was operated upon using a Brunschwig incision under Pentothal and curare supplemented with nitrous oxide and oxygen through an endotracheal tube. A firm mass, about 2.5 cm. at the largest diameter, was found to involve the left wall of the descending duodenum and the adjacent head of the pancreas. This proved, on ultimate examination of the excised specimen, to be a primary carcinoma of the pancreas rather than one arising in the ampulla of Vater or the distal common duct. A radical pancreatoduodenectomy, an appendectomy, and a liver biopsy were carried out. This patient having proved achlorhydric to triple histamine, the scope of the gastric resection consisted of removal of only the distal 6 cm. of the stomach. The entire duodenum, the upper jejunum and the surrounding pancreas, including the uncinate process as well as the head of the pancreas to about the level of the portal vein, were all removed en bloc. Continuity was re-established by anastomosis of the common bile duct end-to-side to the jejunum and the closure of the transected end of the jejunum. The pancreatic duct was anastomosed to the side of the jejunum some 6 cm. below this first anastomosis, and intestinal continuity was restored

between the stomach and the jejunum approximately 40 cm. distal to the biliary anastomosis by the Polya pattern. In addition, a catheter cholecystostomy was carried out with this drainage tube being brought out through an independent stab wound. Closure was with 3-0 silk supported by stitches of No. 24 stainless steel wire through and through, placed about an inch back from the margin of the wound and about an inch apart.

Our pathologist's microscopic report of the material removed indicated that the tumor was composed of poorly differentiated epithelial cells formed into glands, which took a haphazard course and anastomosed with one another. The tumor was in the pancreatic tissue. The surrounding pancreatic tissue showed some evidence of atrophy, but appeared essentially normal otherwise. Five lymph nodes were dissected out and sectioned. These were free of tumor.

Conclusions were carcinoma of the head of the pancreas with common bile duct obstruction; lymph nodes negative for tumor.

The early postoperative period was smooth but characterized by persistent elevation of the blood sugar level which was controlled by the addition of insulin to the intravenous fluid. On March 31, 1949, there was a sharp elevation of the temperature to 103° F. by mouth. Associated with this were symptoms of abdominal discomfort and on careful examination of the operative site, there was noted to be a wound infection in the upper portion of the incision. This area was opened at the bedside, but the patient continued to exhibit difficulty, particularly characterized by some evidence of peritoneal irritation. On April 1 the abdominal incision was opened by removal of two stainless steel wire sutures. Another pocket of pus, measuring about 15 c.c. in volume, was encountered deep in the fat and muscle layers. This was evacuated and exploration continued down through the depths to the site of the anastomoses, which were found to be intact. Penrose and Sump drains were placed in this region. Following this procedure, his condition improved, and the patient was discharged April 20, 1949.

The patient was readmitted on April 23, 1951, with a slight bout of fever which responded rather promptly to antibiotics, and he was discharged on May 10 after a period of further observation. At this time he was in good health and doing very well indeed. The exact cause of this last temperature elevation was not determined, although cholangitis was suspected. Mr. H. has been seen periodically in the Outpatient Department, most recently on Nov. 5, 1952. At this time he was in good health and his stools were normal in color and consistency.

Correspondence with the patient's home physician in August, 1955, indicates that Mr. H. is in apparently excellent health.

Reported Five-Year Survivals After Pancreatoduodenectomy for Cancer.—In his excellent review, Orr[22] states he had found in the literature, or by personal correspondence, four cases of cancer of the head of the pancreas and nine of cancer of the ampulla or papilla with survival of more than five years after pancreatoduodenectomy. Table I represents our amplification of his Table VII.

Diagnosis.—We have been impressed that jaundice due to neoplastic biliary obstruction is associated with pain in more than one-third of instances, and no longer pay great heed to "painless jaundice" as a criterion for consideration.

In the presence of deepening jaundice in the cancer age group and in the absence of laboratory findings suggestive of hepatitis, the four-day feces urobilinogen study of Watson[35] has not misled us to the carcinomatous nature of the obstruction. Watson is currently more cautious than we in this interpretation. At the Kings County Hospital this past year, all nine patients who passed less than 10 mg. of urobilinogen per day in the stool proved to have carcinomatous biliary obstruction.

The technical problem of a four-day stool collection has been simplified by the refrigerated collecting device of Bernstein,[3] which has virtually eliminated both odor and loss of specimens.

TABLE I. LONGER THAN FIVE-YEAR SURVIVALS AFTER PANCREATODUODENECTOMY FOR CANCER OF THE AMPULLARY REGION

AUTHOR	YEAR REPORTED	SITE	SURVIVAL
Whipple	1945	Head (islet cell)	10 years (reported by Parsons[25]
Bartlett	1947	Not stated	5 years
Siler and Zinninger	1948	Ampulla	7 years; died of melanoma
Cattell and Pyrtek	1949	Ampulla	6 years, 2 months
		Ampulla	5 years, 7 months
		Ampulla	5 years, 7 months
Thompson	1949	Ampulla	7 years
Brunschwig	1949	Ampulla	8 years, 9 months
Miller and Clagett	1951	Head	5 years
		Ampulla	5 years
		Ampulla	5 years
		Ampulla	5 years
Child and Ellis	1951	Ampulla	5 years, 3 months
Senff	1951	Head	5 years
Brunschwig	1952	Head	7 years, 3 months
		Duodenum	Over 5 years
Oughterson	1952	Head	5 years (reported by Cliffton)
Harvey	1952	Head	5 years (reported by Cliffton)
Nadal	1952	Head	5 years
Cattell	1954	Head	5 years
Dennis and Varco	1955	Head	9 years, 9 months; died of heart disease
		Head	6 years, 5 months; living and well
		Ampulla	10 years, 3 months; died, apparently of metastases
		Ampulla	9 years, 7 months, living and well
Ripstein	1955	Head	5 years
Allbritten	1955	Head	5 years

Koerte performed a local resection of an ampullary cancer followed by 22 years' survival.
One case of Varco, herein reported (Case 1) is living and well 12 years, 9 months, after a local resection of a carcinoma of the ampulla.

Establishment of the true status at the time of exploration has been facilitated by adequate exposure, freeing of the right border of the duodenum to permit inspection and palpation from behind, inspection of the hepatic artery and mesenteric vessels, and search for metastases to nodes and liver. Biopsy at the time of exploration has not been helpful and has proved dangerous because of continued pancreatic leakage in cases not subjected to resection. Moreover, a positive incisional biopsy probably prejudices the possibility of cure. In addition, there is a further limitation in the value of incisional biopsy in view of the possibility of a false negative report. We have observed several cases in which false negative reports have misled the surgeon and therefore cost the unfortunate patient his chance of cure. In the final analysis, this situation appears to us to be one in which the surgeon must bear the responsibility for the decision whether or not to resect. He cannot here fruitfully delegate it to the pathologist.

Indications for Radical Resection.—Presence of a localized mass without distant evidence of spread has become our indication for pancreatoduodenectomy in cases screened as indicated above.

Pattern of Operation.—We use a one-stage procedure unless there are compelling contraindications. The pattern is that described by us in 1946, in which we remove one-fourth to one-half of the stomach, all of the duodenum, a few centimeters of the jejunum, the head and neck of the pancreas, all the common bile duct, a short segment of the common hepatic duct, and the gall bladder and cystic duct. Preoperative achlorhydria is the rule in this group and permits preservation of most of the stomach. Gastric analysis should, however, be done before operation. Where much free acid is present, a more generous gastric resection is in order. The pattern of reconstruction is shown in Fig. 2.

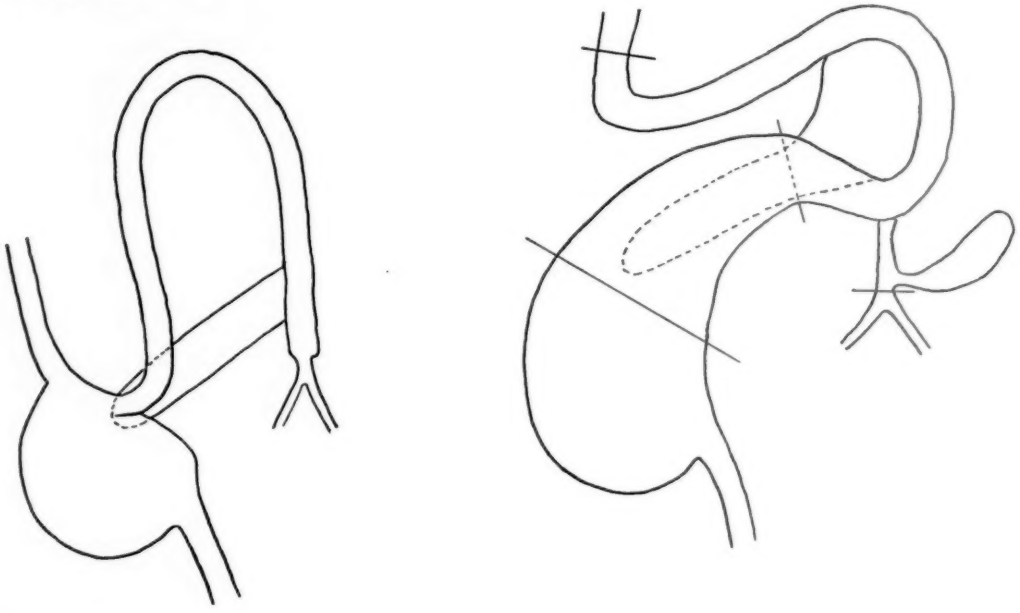


Fig. 2.—Pattern of recommended reconstruction after radical pancreatoduodenectomy. (Redrawn from Dennis and Varco.[11])

Two of the cases reported required twelve hours for the operative procedure. The conviction has grown upon us that meticulous sharp dissection, careful hemostasis, and the fine silk technique pay real dividends in this area. The need for care is emphasized by the great frequency of anomalies in this region. We have encountered two cases in which the hepatic artery has arisen in anomalous fashion, one of them traversing the head of the pancreas; we have encountered a third case in which the superior mesenteric vein passed anterior to the neck of the pancreas. An awareness of the nature and frequency of such anomalies* and great care in recognizing them as well as all normal structures, are both important to success.

*The atlas of Michels is an excellent guide for the surgeon who proposes to work in this field. (Michels, Nicholas A.: Blood Supply and Anatomy of the Upper Abdominal Organs With a Descriptive Atlas, Philadelphia, 1955, J. B. Lippincott Company.)

COMMENTS

Of forty-six cases explored by us and reported in 1946, half were inoperable, and four of the long survivals here reported come from the remaining twenty-three. In this collection of cases, therefore, even though the number of patients is not such as to permit precise conclusions, the five-year survival expectancy is of the same order of magnitude as that in carcinoma of the stomach.[34]

Several authors[8, 18] have expressed the opinion that the finding of a lesion in the ampullary region should be followed by resection even without histologic diagnosis, because it might be ampullary in origin, and therefore much more favorable in outlook. Whipple[37-39] has pointed out that nonfunctioning islet-cell carcinomas of the pancreas follow a very deliberate course, and that patients may survive for many years, even when the lesion has been incompletely eradicated. Even when the possibilities of ampullary and of islet-cell tumors are put aside, we are in emphatic agreement with Brunschwig[6] and with Orr[22] that resection of cancer of the head of the pancreas without distant metastases is the proper procedure. This is true not only because of the five-year expectancy which our figures suggest, but also because of the high risk of palliative surgical procedures as opposed to radical resection,[11, 14, 22] and the longer mean survival after resection than after palliative operations.[11, 14, 22]

Case 3 appears to us to support the thesis that a truly radical resection should be done for apparently localized ampullary tumors. This is all the more true in view of the problems encountered by the pathologist in fixing the origin of many of these growths in resected or autopsy specimens. This thesis is further fortified by the growing list of long-term survivors after such resections who demonstrate that the procedure, properly done, is compatible with good physiologic function.

The extent of the resection and the pattern of the reconstruction which we suggested in 1946 have stood the test of continued use. It is gratifying that Parsons[25] and Pearse,[27, 28] with their extensive backgrounds in this field, have adopted our pattern almost precisely.

As indicated in our report of 1946,[14] autopsy studies in a series of patients dead within a few months after radical resection for cancer of the head of the pancreas called our attention to the frequency with which cancer was found to have extended into the common bile duct. Parsons[25] attributes this finding to flotation of tumor cells in the fluid in the duct, as had first been observed by Cole[12] in the pancreatic duct. Miller and Claggett[19] noted infiltration by way of lymphatic channels in the common duct wall. These observations support the decision to perform the biliary anastomosis, when possible, high in the common hepatic duct, with resection of the duct system below, as a better pattern of good cancer surgery than use of the common duct provides.

One of us described a pattern of reconstruction in 1942[13] in which the gastric anastomosis lay 40 cm. caudad on the jejunum to the end-to-end biliary anastomosis, the aim being to avoid regurgitation of intestinal contents and to provide a wide stoma, in the avoidance of cholangitis, and to avoid the type of

ulceration described by Mann and Williamson[17] at the gastrojejunal anastomosis, a complication which was catastrophic in one of the cases we reported.[14] With the exception of the 40 cm. length of jejunum between the biliary and the gastric anastomoses, this procedure is identical to that reported almost simultaneously by Pearse.[26] Subsequent detailed experimental studies by Pearse and associates[28] indicate that the segment between biliary and gastric anastomoses should be at least 30 cm. long to prevent reflux into the biliary tract.

Cholangitis has been suspected in but two cases in our experience. These are Cases 2 and 4 of this report.

Pancreatic anastomosis, essentially as described by Varco, has been followed in no instance by pancreatic fistulization. It is apparent that several techniques of anastomosis are available, but this has seemed one of the less troublesome aspects of the procedure. Pancreatic anastomosis not only minimizes the chance of pancreatic fistula formation, but has been observed to reduce the difficulty with diarrhea[31] and fat and protein absorption.[40]

Following the observation of Cole[12] that cancer cells can, in some cases, be found floating in the fluid in the dilated pancreatic duct, total resection of the pancreas was recommended by Cattell[8] and by Parsons[25] for cancers of the head of the pancreas. Our own experience with this procedure in a single case was that of widespread implants within three months. It remains to be seen whether the advantages of avoidance of occasional seeding through cells suspended in the fluid will be found to overweigh the known complications of total pancreatectomy.

One of us has followed the suggestion of Moore, Sako, and Thomas,[20] in resecting a segment of the superior mesenteric vein attached to the tumor mass. There were no immediate problems, but the patient returned in a few months with distant metastases, a course similar to that of Moore's case.

One is tempted to consider the five-year survivor of such surgery as cured. Among the cases in Table I, several died shortly after the passage of five years, presumably of their cancers (our Case 3, and cases of Allbritten[1] and Ripstein[29]). The ultimate possibility of true cure, on the other hand, is suggested by Case 2, in which autopsy after death from another cause nine years after resection of a cancer of the pancreas failed to show evidence of residual tumor.

CONCLUSIONS

1. Cancer of the head of the pancreas has apparently been truly eradicated in one case (Case 2).

2. We report two patients with cancer of the head of the pancreas who have survived more than nine years and more than six years, respectively, after resection.

3. We report three patients with cancer of the ampulla of Vater who have survived more than twelve, ten, and nine years, respectively, after resection.

4. Our further experience confirms the conclusions reached in 1946 concerning the management of these cases.

5. The outlook in these tumors, both pancreatic and ampullary, appears not to be appreciably worse than the outlook in cancer of the stomach. It is likely that application to pancreatic lesions of the current vigorous approach utilized by Wangensteen in the problem of cancer of the stomach will lead to substantial improvement in that outlook.

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DIFFERENTIAL SECTION OF THE SPINOTHALAMIC TRACT TO RELIEVE PAIN FROM CARCINOMA OF THE BREAST

LYLE A. FRENCH, M.D., GERALD L. HAINES, M.D. (BY INVITATION), AND WILLIAM S. OGLE, M.D. (BY INVITATION), MINNEAPOLIS, MINN.

(From the Department of Surgery, Division of Neurosurgery, University of Minnesota Medical School)

THIS is a discussion of our investigations into the problem of differential section of the spinothalamic tract to obtain relief of pain in the areas generally involved in carcinoma of the breast. These areas are the dermatomes extending from the fourth cervical level down to about the eighth thoracic level and including not only the area of the breast itself but also the adjacent areas into which cancer may spread, such as the supraclavicular region, the axilla, and the adjacent pleura. This area is not rendered analgesic with cordotomy done at the usual site, the second thoracic level. To obtain analgesia up to the fourth cervical level it is necessary to make the cord incision at the second cervical level. The usual section at this level results, however, in analgesia not only over the arm and chest but also the abdomen, leg, and foot which are areas usually not involved with carcinoma of the breast. The advantages of being able to section differentially the spinothalamic tract at the high cervical region are obvious, for this would make possible a selective analgesia of the involved areas, leaving sensation intact in the lower extremity. This investigation was undertaken in order to determine if, by differential section, a selective zone of analgesia could be established with sufficient ease and certainty to warrant more general utilization of the technique, and to determine if the area of analgesia thus obtained was permanent and without "islands" of hypalgesia.

Since Spiller and Martin[8] introduced spinothalamic tract section, many investigators have considered the possibility of making a differential section. Most of these sections have been made in the upper thoracic levels. Frazier,[2] in 1920, recommended an incision 2.5 mm. deep, beginning immediately anterior to the dentate ligament and extending to the anterior root. He found that such an incision made at levels varying from T_2 down to T_5 produced analgesic levels that were relatively low, usually not above the lower lumbar dermatomes. In 1926 Peet[6] stressed that a more anteriorly made incision, that is, an extension of the incision anterior to the base of the anterior root, resulted in the attainment of a higher sensory level. Foerster and Gagel[1] confirmed Peet's findings and proposed that the fibers comprising the spinothalamic tract are arranged in a laminated fashion, those from the lowermost segments of the body occupying a place at the periphery of the tract and those of the higher segments disposing themselves toward the center of the cord. This arrangement was generally accepted until Hyndman and Van Epps[3] in 1939 and Walker[9] in 1940 demonstrated that the sacral segments are not only displaced laterally but also posteriorly as they ascend in the lateral spinothalamic tract so that the fibers

representing the lower segments of the body are located in the posterolateral part of the spinothalamic tract and fibers representing successive segments upward are disposed more anteriorly. Hyndman and Van Epps,[3] by differential section of the spinothalamic tract at the T_2 level, were able to eliminate pains in the chest and abdomen without including the lower extremities. They emphasized that these less extensive incisions are followed by a lower morbidity and fewer sequelae. But in these and other studies there seemed to be considerable variability in results. Kahn and Peet[4] in 1948 concluded that this was due to variation in the location of the spinothalamic tract in relation to the anterior root. They showed that the anterior root does not always correspond to the downward or medial prolongation of the anterior horn, which had been felt to be the anterior limit of the spinothalamic tract, but that the anterior root often is more laterally placed. Their work also was done principally for cordotomies at the second thoracic level, but they did investigate the possibility of doing them at the second cervical level. By anatomical studies they found at both the T_2 and C_2 levels that the distance from the anterior median fissure to the center of the emergence of the anterior root circumferentially was 4 to 5 mm. and the distance from the anterior roots to the dentate ligament was about the same. The anterior extent of the spinothalamic tract extends 2 to 3 mm. anterior to the line of emergence or base of the anterior root. They found it necessary to carry the incision well anterior to the anterior root to obtain, with certainty, high levels of analgesia.

Roulhac[7] and Morin, Schwartz, and O'Leary[5] have reported extensive clinical and investigative experience with cordotomy at the C_2 level. The cord incision made by them begins at, or just posterior to, the dentate ligament and, as a general rule, is carried no further forward than the anterior root, thereby cutting only the posterolateral two-thirds of the quadrant. This incision usually has not produced an analgesic level above T_5 or T_6. Presumably, therefore, the uncut area anterior and medial to the anterior root contains the fibers from the upper thoracic and cervical regions. This is consistent with the data to be presented here in which the fibers subserving the upper thoracic and cervical areas are more medially and anteriorly located, that is, medial to the anterior root. It is emphasized, moreover, that there is considerable variation in the compactness of the tract so that apparent identical cord incisions do not always produce identical sensory loss.

This report includes (1) the results of differential section of the spinothalamic tract at the C_2 level in a series of experimental animals; (2) observations on selective section of the tract at this level in humans under local anesthesia; and (3) results of application of these data to humans operated upon under general anesthesia.

In a series of six Macaca monkeys incisions were made into the anterolateral quadrant of the spinal cord at the C_2 level. These sections were made differentially so that in one group only the posterior part of the quadrant was cut, that is, the area immediately anterior to the dentate ligament; in another group only the very anteromedial part of the quadrant was sectioned, and in a third group almost the entire quadrant was sectioned. The animals were tested for analgesic areas, following which they were sacrificed and serial sections made of the cervi-

cal cord. Because of the difficulties in exposure, adequate landmarks, and size of the cord at this level, the area sectioned did not always correspond to that intended. Even so, an attempt was made to correlate the site of the incision with the neurological loss and, in spite of these difficulties, a reasonably consistent correlation was found. Fig. 1 reveals an incision that produced analgesia from the C_3 to the T_5 level. The lower level in this animal was indefinite but there was an unquestionable foot and leg sparing. Fig. 2 reveals the incision

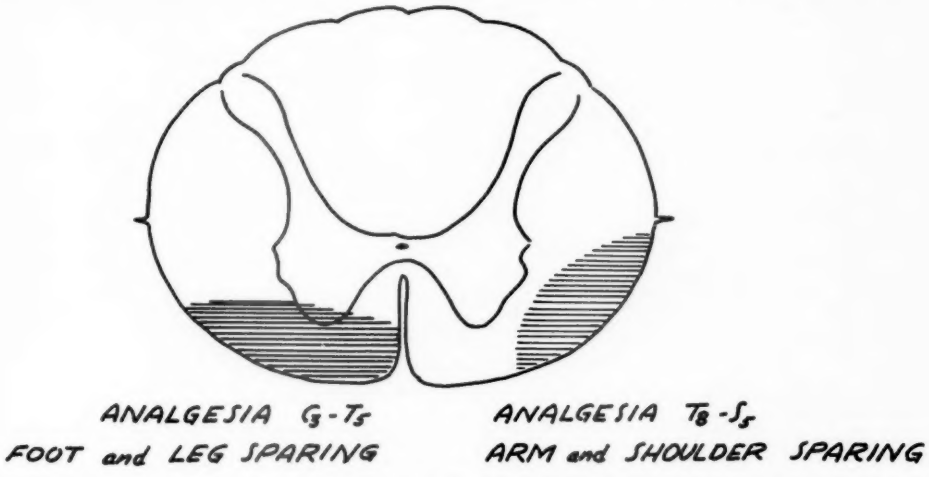

Fig. 1.—Cord incisions at C_2 level in Macaca monkeys producing analgesia as recorded above.

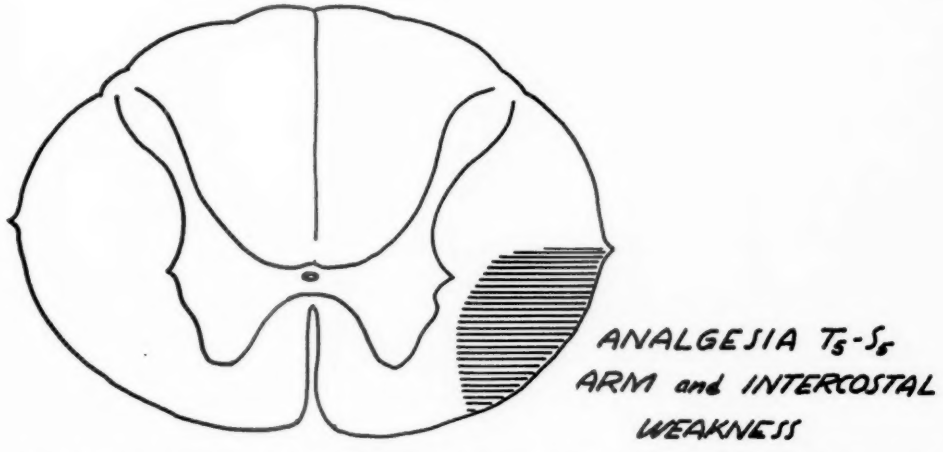

Fig. 2.—Cord incision at C_2 level in Macaca monkey with resultant analgesia from approximately T_5 caudad. The corticospinal tract was injured by the incision which began at or just behind the dentate ligament.

that produced analgesia up to about the T_5 level. There was no apparent sparing up to this level. Comparing the data obtained from these two groups it seems that the foot (sacral) fibers must lie in an area immediately anterior and medial to the dentate ligament (the posterior and lateral part of the spinothalamic tract) and the arm (cervical) fibers in the areas around and medial to the anterior root (medial and anterior part of the spinothalamic tract). Cord sections made at this level in other animals in this series produced analgesic areas reasonably confirmative to the above findings.

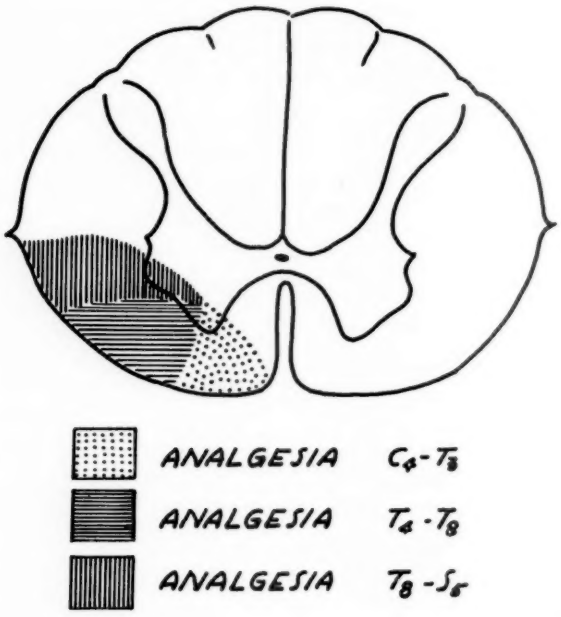

Fig. 3.—Anterolateral cordotomy at C_2 in humans under local anesthesia. The extent of incision in anterolateral column is shown in relation to the area made analgesic.

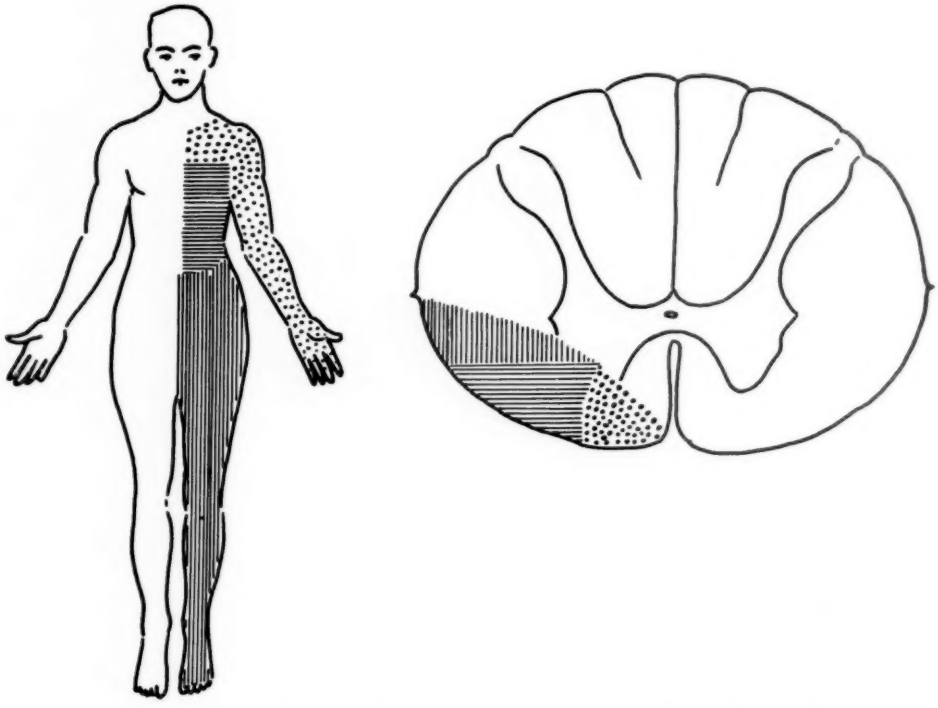

Fig. 4.—Anterolateral cordotomy at C_2 level in humans under local anesthesia. Area of body made analgesic by the selective sections is shown. In other patients the extent of the incision necessary varied but there was a definite general pattern for the location of the fibers from specific body areas.

The second part of this investigation was the differential sectioning of the anterolateral quadrant and the testing of a series of twenty-seven patients operated upon under local anesthesia. Figs. 3 and 4 reveal areas made analgesic with restricted tract sections in two of the patients. It is emphasized again that the variability in the spinothalamic tract found by others was experienced in these investigations. In general, however, there seemed to be a reasonably consistent general pattern of location for the fibers from the specific body areas. This permitted us to continue for additional verification.

Fig. 5.—Photograph of patient with carcinoma of breast. Area with vertical lines was made anesthetic by rhizotomy of C_{2-4} and area with tangential lines was made analgesic with differential anterolateral cordotomy as explained in text.

In the third part of this investigation the data culled from the first two parts were tested clinically by the purposeful differential section of the spinothalamic tract in human beings under general anesthesia. This was done in a series of four patients with malignant neoplasms and severe intractable pain in the shoulder, arm, or upper chest. All tolerated the procedure well. There

were no complications. The follow-up period ranges from six to twenty-seven months. Postoperatively all have been free of the pain previously present. Figs. 5 and 6 show the area made analgesic with an incision made for this purpose. In this patient the cataract knife entered the cord about 2 mm. lateral to the anterior root. The incision was carried directly medially for a distance of 6 mm. and then anteriorly to the pia. In order to preserve with certainty the integrity of the anterior spinal artery the most medial portion of the incision was made by clamping with a pointed forceps. Similar incisions were made in the other three patients and the resulting analgesic areas were comparable.

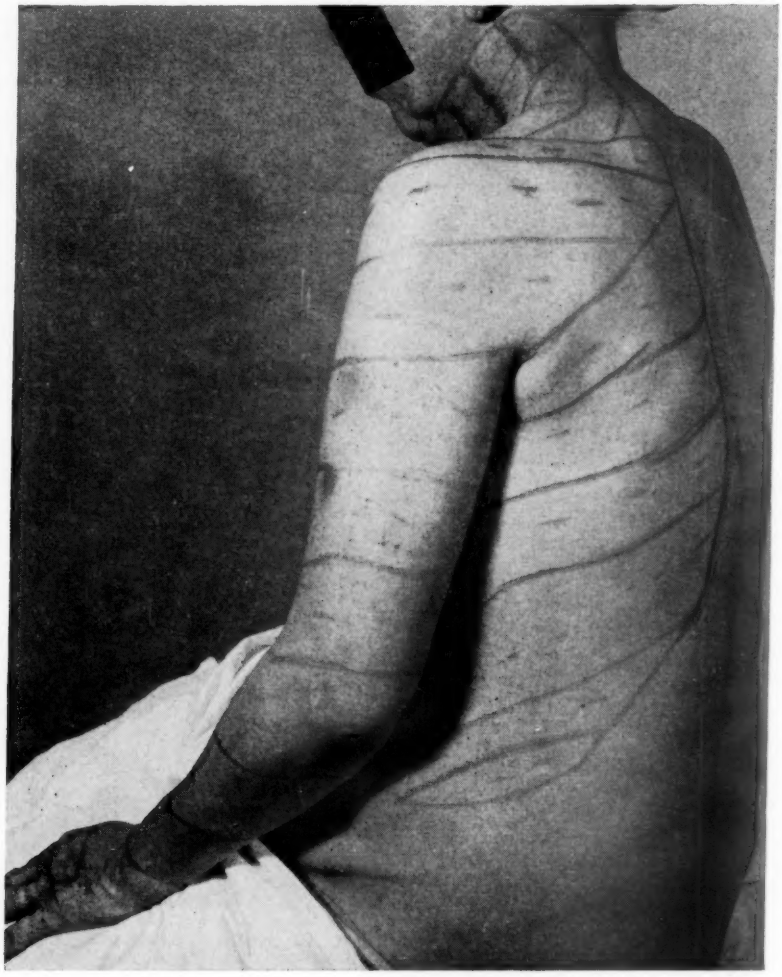

Fig. 6.—Photograph of same patient as in Fig. 5, showing analgesic and anesthetic areas.

SUMMARY

1. Experimental data are presented demonstrating a specific pattern of location within the spinothalamic tract of fibers carrying pain sensations from various regions of the body.

2. Differential section of the spinothalamic tract has been used successfully in a small series of patients with carcinoma producing severe intractable pain in the arm, supraclavicular region, or upper chest.

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SURGICAL MANAGEMENT OF GASTRIC POLYPS AND ADENOMAS

LYLE J. HAY, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery of the University of Minnesota Medical School and Mount Sinai Hospital)

THE establishment of adequate information on the relationship of the precursor lesion, gastric adenoma, to gastric cancer should be one of the essential steps in lowering the death rate from gastric malignancy. The elimination of these lesions requires gastrotomy, partial gastrectomy, or even total gastrectomy. Often the decision for operation is based on symptoms of obstruction or bleeding. More often the lesion is found in the routine examination of patients without ominous symptoms, and the decision for operation must be based on the probability of the polyp being malignant or becoming malignant. A single gastroscopic or roentgenologic examination may not be adequate to determine the probable benign nature of the lesion or even to establish the diagnosis of a probable adenoma as contrasted to a foreign body, hypertrophic gastritis, or leiomyoma. In two patients, A. M. and A. T., a delay in operation for cancer for nine and thirteen months, respectively, was caused by the inability of the examiners to diagnose a definite malignancy and thus persuade these two women, 76 and 79 years of age, to have operations. Fortunately both survived operation by a period exceeding seven years. This report giving further information on the history of "benign" adenomas should provide valuable information to aid the clinician.

Polyp will be used to describe the lesions clinically diagnosed and adenoma to describe the lesions pathologically proved.

The group of patients previously reported have been traced for five additional years. The groups will be presented as they were in the original report. Thus, Group 1 contains the patients treated by observation. The patients who have been operated upon in the five-year interval will be noted and summarized.

Prognosis.—The benign nature of gastric polyps is attested to by the fact that none of the patients with benign polyps developed symptoms of obstruction or bleeding during this five-year period. The several operations performed were carried out because of the probability of malignant change.

Table I shows the group of 11 patients with polyposis. None of these patients developed gastric cancer in eighty-eight patient years. Two patients were operated upon for gastric polyps after five and six years of observation, respectively.

This presentation is based upon work done under The United States Public Health Service Grant C-298 (C5).

Table II shows the 26 patients with one or two polyps. Patient N. J. died of a gastric cancer (Case 3).[1] No other gastric cancers have developed in 157 patient years. Two patients had polypectomy after four and nine years' observation, respectively.

TABLE I

GROUP	NUMBER	AVERAGE AGE	RANGE OF FOLLOW-UP	TOTAL	AVERAGE	FINDINGS	DEATHS
1	11	71.8	5 to 15 years	88	8.8*	No cancer	3†

*One patient who died in his sleep one year following diagnosis of polyp was eliminated from this calculation.

†Two patients, 77 and 78 years of age, including the patient who had polypectomy, died of heart attack. The patient who had a total gastrectomy died of malnutrition a few months after operation at 56 years of age.

TABLE II

GROUP	NUMBER	DURATION RANGE (YEARS)	TOTAL	AVERAGE	CANCER OF STOMACH
2	26	4-13	157	7.85*	1†

Two patients had polypectomy performed after four and nine years of observation. Benign adenomas were found and the patients were well four and two and one-half years later.

*Six patients, who died of lymphoblastoma, carcinoma of the breast, uremia, automobile accident, cerebrovascular accident and sudden death with cause unknown, were eliminated from this calculation.

†This is the patient, N. J., previously reported as dying of carcinoma.

Table III is a composite of the single and multiple adenoma groups treated by gastric resection. Patient A. F. developed a gastric cancer in the residual stomach four years following operation.[1] No cancers developed in the five-year interval. One patient, S. B., had polyps removed from the residual stomach eleven years after subtotal resection and is well two years later.

TABLE III

	NUMBER	AVERAGE AGE	DURATION OF FOLLOW-UP (YEARS)		MALIGNANT CHANGE	REOPERATION	PATHOLOGY AT SECOND PROCEDURE
			TOTAL	AVERAGE			
FROM GROUPS 5 AND 6	15	69	82	5.8	0	0	
	8	66	49	6.1*	1†	1	Benign

*One patient died of operation and was eliminated from this calculation.

†Patient O. F., previously reported, developed a carcinoma in the residual pouch.

Table IV summarizes the 9 patients with adenomas treated by polypectomy. No patients developed malignancy in sixty patient years. One patient had polypectomy for what proved to be a benign adenoma.

TABLE IV

NUMBER	AVERAGE AGE	DURATION OF FOLLOW-UP* (YEARS)		RESIDUAL OR NEW LESIONS	REOPERATION	PATHOLOGY
		TOTAL	AVERAGE			
9	72.2	60	7.5	2	21	Benign adenoma

*One patient, S. R., who had polypectomy during operation for a rectal cancer from which she died one year later, was not included in the calculation.

Table V indicates that five of the 27 patients treated by resection for malignancy survived over five years.

TABLE V. PATIENTS WITH CARCINOMAS ASSOCIATED WITH ADENOMAS APPARENTLY ORIGINATING FROM ADENOMAS OR OF A SIZE OR CONFORMATION MAKING DIFFERENTIATION DIFFICULT

GROUPS	NUMBER	FIVE-YEAR SURVIVAL	POSITIVE NODES IN SURVIVORS
3 and 7	27	5	1

Table VI summarizes the experience with the 70 patients diagnosed as having benign gastric polyps. The 2 cancers noted developed within four years of the original diagnosis. All 6 of the patients operated upon in the past five years had benign adenomas.

TABLE VI

	TOTAL	TREATED BY OBSERVATION	GASTRIC RESECTION	POLYPECTOMY
Number of patients	70	37	23	10
Number of patient years	432	245	127	60
Number of cancers	2	1	1	0
Patients operated or reoperated upon in 5 years	6	4	1	1
Operative deaths	1	0	1*	0

*One other patient, G. J., died of malnutrition a few months after total gastrectomy.

Table VII summarizes the data on the 12 pernicious anemia patients observed with a diagnosis of benign gastric polyps. No gastric cancers developed in this group.

TABLE VII. LONG-TERM FOLLOW-UP OF PERNICIOUS ANEMIA PATIENTS WITH GASTRIC POLYPS

	SEX	AGE	DURATION OF POLYP IN YEARS	DURATION OF PERNICIOUS ANEMIA IN YEARS
Multiple Polyps				
J. M.	M	82	9	19
O. T.	F	62	6	6
Single Polyps				
L. C.	M	62	9	9
J. C.	M	78	9	16
E. L.	F	73	8	9
E. G.	F	62	7	18
M. C.	M	76	12	13
E. H.	F	82	10	15
F. M.	M	69	5	5
A. T.	F	69	7	7
C. C.	M	76	13	20
I. H.	F	60	15	25
			Total 110	Total 162
			Average 9.17	Average 13.5

No cases of malignancy were observed.

Table VIII summarizes the patients operated upon during the past five years. Patient L. C. was operated on because of enlargement of the polyps from less than 1 cm. to 2.5 cm. in diameter. Patient J. E. had a cluster of 3 adenomas and these were thought to be enlarged. The specific reason for operation on the other four patients is not clear from the patient records, but was undoubtedly related to the malignant potential of gastric polyps.

TABLE VIII. PATIENTS OPERATED UPON SINCE LAST STUDY

NAME	SEX	AGE	OPERATION	PREVIOUS OPERATION	PATHOLOGY	PREOPERATIVE DURATION	RESULT
L. M.	F	77	Polypectomy	None	2 adenomas 7 mm. in diameter	5 years	Died of heart attack 1 year postoperative
G. J.	M	56	Total gastrectomy	None	Several adenomas up to 2 cm. in diameter	6 years	Died of malnutrition few months postoperative
S. B.	F	66	Polypectomy from gastric pouch	Subtotal gastric resection	3 adenomas up to 2 cm. in diameter	11 years	Living 2 years; no residual polyps
J. E.	M	73	Subtotal resection	Polypectomy	3 adenomas up to 2 cm. in diameter	11 years	Living 5 years; no residual polyps
L. C.	M	78	Polypectomy	None	1 adenoma 2.5 cm.	9 years	Living
W. G.	M	71	Polypectomy	None	2 adenomas 1 cm. in diameter	4 years	Living four years; no residual polyps

DISCUSSION

The frequent association of benign gastric adenomas and gastric cancer as well as the occasional finding of a malignant area in a benign adenoma establishes the precancerous nature of gastric adenomas. Occasional cases have been reported where carcinoma was found in the location of a previous gastric polyp. Patient A. T. in this report is one of these.

Earlier reports of the frequency of malignant change in large gastric polyps ranging from 9 to 40 per cent were correct.[1-3] However, since more roentgenographic and gastroscopic studies of the stomach are done in patients with mild symptoms, the small asymptomatic polyp is being recognized. The chance of malignancy in these is less. Only one of the 81 lesions less than 2 cm. in diameter was malignant while 6 of 14 lesions over 2 cm. in diameter were malignant.

Our experience would indicate that a diagnosis of a benign polyp by the roentgenologist and/or gastroscopist is rather reliable. Repeat examination of the presumed benign lesions for growth, infiltration, or other signs of malignancy during the first year or so will minimize diagnostic errors.

TREATMENT

Nonoperative Treatment.—The nonoperative or observation type of management is recommended in asymptomatic or mildly symptomatic patients with polyps less than 2 cm. in diameter which appear benign to the gastroscopist and roentgenologist. These patients are observed by roentgenologic or gastroscopic examination every three or four months for the first year and then biannually. The probability of malignancy as indicated by an increase in size of the lesion, infiltration of the gastric wall, or increased nodularity and pallor of the surface of the lesion indicates the need for operative treatment.

Operative Treatment.—The following groups of patients should be subjected to operation: (1) patients with polyps larger than 2 cm. in diameter; (2) patients with polyps smaller than 2 cm. in diameter in which the roentgenologist or gastroscopist suspects malignancy; (3) patients with clinical symptoms due to polyps if the symptoms are of a severity to justify the risk of operative intervention; and (4) patients who refuse or are unable to accept adequate observation because of geographic or personal reasons.

Subtotal Gastric Resection.—The resection of 75 to 85 per cent of the stomach is recommended as the routine operation where surgery is indicated. Subtotal gastric resection is recommended even for single lesions when accompanied by achlorhydria or mucosal atrophy. Most of these lesions are adenomas and a gastric resection removes adjacent atrophic mucosa and undetected adenomas with their malignant potential, and provides an adequate cancer operation where malignancy is present. The one major exception to this routine has been in patients having polyps in the cardia. In these individuals an anterior gastrotomy should be made and the lesion of the cardia removed. The lesion should be subjected to immediate "frozen section" and histologic examination. If the lesion is benign and solitary, polypectomy with removal of a rim of

mucosa about the base should be performed. If multiple lesions are present in the cardia a total gastrectomy is indicated. If the lesion of the cardia is malignant, a total gastrectomy with removal of the lesser and greater omentum and a splenectomy is indicated.

CONCLUSIONS

1. The potential to malignant degeneration in small gastric polyps is less than the older literature indicates.

2. Careful gastroscopic and roentgenologic examinations make the diagnosis of benign polyps possible within a reasonable margin of error.

3. Small gastric adenomas are much less likely to be malignant than large ones. The size of adenomas is probably the most valid criterion for determining malignancy.

4. Observation management of patients diagnosed as having small benign polyps is justified if they can be observed at frequent intervals.

5. Pernicious anemia patients with small gastric polyps may have a smaller potential for gastric cancer development than we thought.

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A SUMMARY OF RESEARCH TECHNIQUES FOR INVESTIGATING THE CIGARETTE SMOKING–LUNG CANCER PROBLEM

GEORGE E. MOORE, M.D., PH.D., AND FRED G. BOCK, M.S., BUFFALO, N. Y.

(From the Roswell Park Memorial Institute)

ONE of the most popular medical controversies of the day is the question of whether or not cigarette smoking is a causal factor in the rapidly increasing incidence of lung cancer. This paper presents a brief review of the clinical and experimental investigative techniques which have been used and others which might be of value in solving this problem.

CLINICAL STUDIES

Although such a relationship had been suggested for many years, the era of large epidemiological studies of this problem was initiated in 1950 by the reports of Levin,[15] Wynder,[23] and Doll and Hill.[5] Approximately 30 papers concerned with various aspects of the frequency and/or incidence of lung cancer among cigarette smokers have been published. The majority of these papers has concluded that a significant association exists. (For those interested in a summary of these studies and a review of the general biologic effects of tobacco, the recent book edited by Wynder[22] is recommended.)

The most extensive study in this country was that undertaken by Hammond and his colleagues[9, 10] with the support of the American Cancer Society. Briefly, this study concerned the smoking habits of 187,766 white men between the ages of 50 and 69, which were obtained by personal interviews conducted by volunteers. Subsequently, records were kept of all deaths occurring in the interviewed group. The latest report of this study included follow-up data for a period of 32 months, during which time there were 285 deaths attributed to carcinoma of the lung. Tables I, II, and III, taken from data in Hammond's paper, compare the standardized death rate per 100,000 population for nonsmokers and smokers.

The authors conclude that their data indicate not only an association between cigarette smoking and lung cancer, but a cause-and-effect relationship. Even though this study is prospective in design and, therefore, less likely to have hidden bias, it has not escaped criticism.

Berkson[2] has recently criticized all of the various reports on this subject and suggested that perhaps some selective mechanism or bias has been inadvertently introduced. The existence of some bias in individual studies is recognized by most investigators. It would seem strange, however, if such selective factors would be present to the same degree in both prospective and retrospective studies. Other criticisms in this report seem injudicious.

An example of a retrospective study is that of Levin in which the studies at Roswell Park Memorial Institute are reviewed and compared with data obtained by the New York State Health Department. It is of interest to note that the age-adjusted lung cancer mortality among males in New York State has increased 385 per cent between the period 1931 to 1933 and 1948 to 1950.

TABLE I. CARCINOMA OF LUNG DEATHS
(Standardized death rates per 100,000

Nonsmokers	33.4
Regular cigarette smokers	245.5
Pipe smokers only	74.6
Cigar smokers only	36.3

TABLE II. COMPARISON OF STANDARDIZED DEATH RATES FROM ADENOCARCINOMA, AND CARCINOMA OF THE LUNG EXCLUDING ADENOCARCINOMA

	ADENOCARCINOMA	CARCINOMA OF LUNG (EXCLUSIVE OF ADENOCARCINOMA)
Nonsmokers	6.0	4.9
Cigarette smokers	17.3	145.0
Pipe only	16.3	49.0
Cigar only	4.9	26.4

TABLE III. CARCINOMA OF THE LUNG DEATH RATES ACCORDING TO AMOUNT OF CIGARETTE SMOKING

Never smoked	33.4
Former smokers	
none at time of survey	101.8
occasionally	140.8
Less than one-half pack per day	217.8
One half to 1 pack per day	212.8
One to 2 packs per day	430.8
Over 2 packs per day	734.1

FURTHER EPIDEMIOLOGICAL RESEARCH

Levin[14] has concluded that total population studies would probably give more precise estimates of the risk associated with smoking but he does not expect that such studies can furnish more information regarding the epidemiologic significance of smoking unless accompanied by a parallel study of all non-etiological and suspected etiological factors among smokers and nonsmokers.

It is interesting to note that the data from Hammond and Horn's study[10] indicate that the dangers of smoking in regard to coronary disease are more important than the lung cancer problem from a public health standpoint. Certainly, there is no evidence to suggest that the etiological agent, if there be one, is common to both diseases.

Unpublished studies from Roswell Park Memorial Institute have confirmed other reports[20] that reveal a higher death rate among smokers from cancers of sites other than the lungs. This finding has been used by critics as indicating a bias in the studies. However, it might be equally true that this higher frequency of cancer has resulted from the exposure of other organs in the body to a carcinogenic agent. It is interesting to note that the sites which are directly

exposed to tobacco or tobacco products are also the sites with an increased cancer later on. It is also hoped that future studies will more clearly indicate whether there is a real sex difference in the susceptibility to lung cancer.

THE SIGNIFICANCE OF CHEWING TOBACCO STUDIES

An interesting series of reports through the years have associated the habitual use of tobacco or tobacco and other ingredients such as the Betel nut with a high incidence of oral cancer. Eisen[6] noted that the natives in the South Pacific chew Betel products without additives and that of 8,000 native hospital admissions, only one case of squamous cancer of the oral cavity was noted. In contrast, Khanolkar[12] reported that in a series of 2,880 cases of proved carcinoma seen at the Tate Memorial Hospital in Bombay, India, there were 1,000 cases of intraoral cancer. It is noteworthy that in contrast to the natives of the South Pacific, tobacco leaves or tobacco products are commonly used in India in conjunction with the use of Betel nuts or leaves, lime from granite or seashells, and other additives.[19] The possible ancillary roles of chronic irritation and vitamin deficiencies are yet to be evaluated. More recently, Sanghvi[21] has reported a statistical study again indicating the significance of tobacco use in the development of oral carcinoma.

In this country, there has been little interest in this problem. Friedell and Rosenthal[8] reported 8 cases of intraoral carcinoma in elderly individuals who had used chewing tobacco for about fifty years. They noted that the tumor sites coincided with the area where the quid was constantly held. A similar observation has been made by Khanolkar and Suryabai[13] where cancer of the inner surface of the lip is common among inhabitants of the Bihar district who place the tobacco between the gum and the lip. More recently, Ackerman[1] included in a report on verrucous carcinoma of the oral cavity a note that 11 of 18 patients who had lesions on the buccal surface were inveterate tobacco chewers. In common with other authors, they also emphasized the probable significance of poor oral hygiene, carious and jagged teeth, and accompanying leukoplakia.

Moore, Bissinger, and Proehl[17] summarized a study of men over 50 years of age who had been queried as to their smoking habits and chewing tobacco experience. It was concluded that there was a significant association of the habitual use of chewing snuff or tobacco for more than twenty years with the occurrence of leukoplakia, cancer of the buccal mucosa, floor of the mouth, and alveolar ridges.

COMMENT

Incomplete studies from this Institute indicate that the use of chewing tobacco is probably more highly associated with carcinomas of the pharynx and esophagus than is cigarette smoking. It would seem logical to predict from these various studies that the site of malignancy should be related to the direct exposure of the carcinogen, particularly if organ susceptibility is comparable, and, therefore, one would expect that cigarette smokers would be more likely to have a higher incidence of carcinoma of the larynx and lung whereas pipe

and cigar smokers and chewers, all of whom swallow an appreciable amount of tobacco and tar, would be more likely to develop lesions of the mouth, pharynx, extrinsic larynx, and esophagus.

Certainly, the route of excretion of the carcinogen should also be checked, since if, for example, it is largely excreted by the kidneys, one might expect the development of bladder tumors. Unpublished studies by us revealed increased frequency of tobacco chewers among patients with bladder cancer but not with cancer of the prostate.

Table IV depicts a theoretical cancer site for the various modes of tobacco usage based upon published studies, and investigations here at Roswell Park.

TABLE IV. THEORETICAL SITE INVOLVEMENT BY MALIGNANCY ACCORDING TO MODE OF TOBACCO EXPOSURE

CIGARETTE	PIPE	CIGAR	CHEWERS
1. Lungs and bronchi	1. Lip	1. Alveolar ridge	1. Intraoral
2. Larynx (intrinsic)	2. Intraoral	2. Intraoral sites	a. Buccal mucosa
3. Intraoral	a. Palate	3. Pharynx and extrinsic larynx	b. Alveolar ridge
4. Pharynx	b. Tongue	4. Esophagus	c. Floor of mouth
5. General effects (especially in heavy smokers)	c. Floor of mouth		2. Pharynx, tonsil, and extrinsic larynx
	3. Pharynx, tonsil and larynx (extrinsic)		3. Esophagus
	4. Esophagus		4. Facial*
	5. Lung		5. Bladder*
			6. General effects (especially in heavy users)

*In several of our preliminary studies (not considered statistically valid), chewers had increased frequency of carcinomas at these sites.

A study of the tables and the reports summarized in the preceding section suggests these additional hypotheses: (1) A carcinogen, if present, must be inherent in the tobacco itself rather than in paper, or additives, or as a result of the "curing" and other processing. (2) The factor is probably a very "weak" carcinogen and, therefore, must be present in large amounts over a long period of time to cause biological alterations. (3) The tobacco does not have to be combusted to be carcinogenic, but tobacco tar is probably more active as a result of concentration of the active factor. (4) The most susceptible sites are mucosa surfaces directly exposed to whole tobacco or tars. Protected mucosal surfaces such as the gastric mucosa probably will not be found to be susceptible. (5) The active factor is not a metabolic product. (6) Deficiency states probably increase the susceptibility of mucosal surfaces to malignancy.

FUTURE STUDIES

Recently, there have been several reports of pathologic studies of bronchi removed at autopsy which showed a significant degree of mucosal thickening and hyperplasia in heavy smokers. Additional studies of the larynx are indicated as well.

Unfortunately, it seems difficult, if not impossible, to carry on direct experimental studies in human beings since the active factor is obviously weak and observations of at least twenty years' duration would probably be necessary.

Attempts to set up experiments utilizing prisoners or other volunteers to evaluate sensitivity phenomena, reactions to skin painting, and so forth, should be seriously considered.

BIOLOGICAL INVESTIGATIONS

Introduction.—Most biologists are well aware that data obtained from animal experiments indicating that there is or is not a carcinogenic agent in tobacco are not directly pertinent to the human problem. For example, it is well known that some compounds are extremely carcinogenic in rodents and apparently not carcinogenic in primates. The reverse situation is also true. However, the biologic and chemical investigations should be important in the identification of agents which must be regarded with suspicion. These agents should probably be removed from the tobacco before human consumption, even considering the foregoing reservations. Because of variation in species susceptibility, it would be advisable to test a large number of animals. However, practical considerations have limited most studies to laboratory rodents. The additional factor of a possible sex difference should be studied.

A list of the experimental procedures which might be of value in attacking such a problem follows:*

EXPERIMENTAL BIOLOGICAL TECHNIQUES

1. *Skin Painting Experiments:*
   a. Whole tobacco tars from smoking machines.
   b. Tobacco fractions obtained by solvent extraction.
   c. The application of tumor-initiating agents such as a hydrocarbon or x-ray.
   d. The coincidental application of promoting agents such as croton oil.
2. *Ingestion Experiments:*
   a. The feeding of mixtures of powdered tobacco products and standard diets.
   b. Tobacco-diet mixtures with vitamin-deficient synthetic diets.
   c. Tobacco which has been extracted with various solvents.
   d. Addition of water-soluble tobacco fractions and individual constituents such as nicotine to the drinking water.
3. *Injection Experiments:*
   a. Subcutaneous injection of whole tar and tar fractions.
   b. Injection of certain organs with extracts, i.e., the use of thread inpregnated with tar.
   c. The injection of embryonic tissues with tobacco fractions such as the use of embryonic lung tissue.
   d. The exposure of heterologous tissues such as human embryonic lung tissue grown in the rat and hamster.
4. *Inhalation:*
   a. Introduction of cigarette smoke into large chambers containing mice.
   b. Techniques to provide direct inhalation of smoke by individual animals.
   c. Exposure of bronchial epithelium by tracheotomy to inhalation, direct painting with tars, etc.

Indirect Screening Techniques.—Many indirect tests have been suggested as screening adjuncts to find fractions which may have carcinogenic activity. Most biologists are agreed that such tests are useful but have no significance as

*Many of these experimental techniques were discussed at the lung cancer conferences sponsored by the American Cancer Society.

proof of carcinogenicity. The following techniques have been considered to be of value in the tobacco problem: (1) Microbiology—The use of microbiologic techniques to determine mutation rates, growth suppression, and so forth. (2) Biochemistry—The effect of tobacco fractions upon enzyme systems, chemical relationship to known carcinogens. (3) Mutagenic effects upon Drosphila, protozoa, plants, and so forth. (4) Teratogenic effects in experimental animals. (5) Secondary histological changes—Sebaceous gland suppression, induction of leukoplakia, hyperplasia, and so forth.

Chemical Analysis.—One of the large areas of intensive investigation is the chemical study of tobacco. It is noteworthy that some chemists do not report differences in the fractions prepared from tobacco tars from smoking machines and fractions from unburned tobacco.

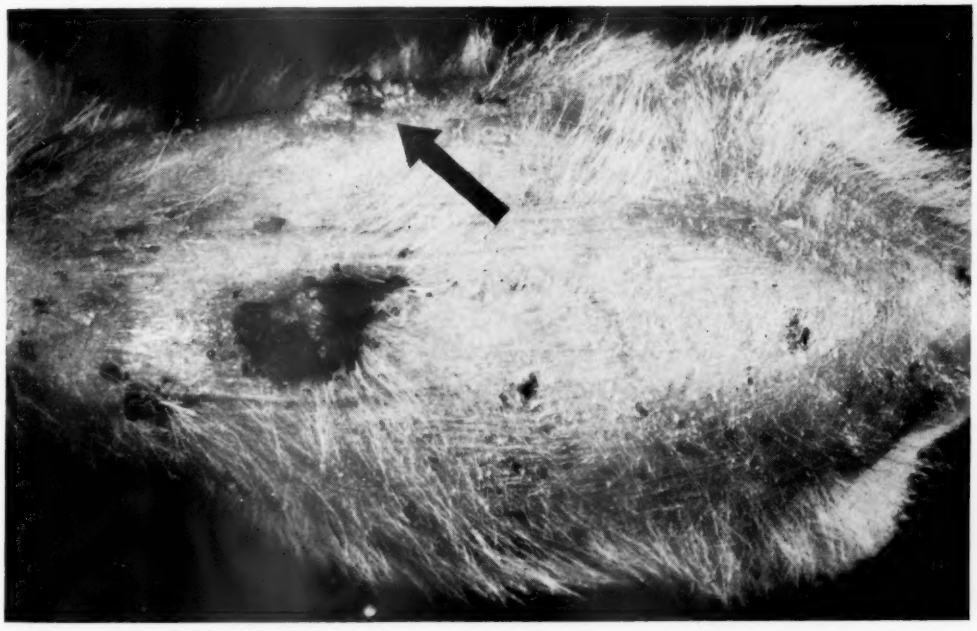


Fig. 1.—Photograph of a mouse painted 3 times a week with a smoke tar-acetone solution. After ten months many papillomas are present and an infiltrating squamous carcinoma (indicated by arrow).

Several investigators have indicated they have identified benzpyrene from both cigarette paper and tobacco itself. Recently, Cooper and Lindsey[4] reported 4.0 μg of benzpyrene in the smoke of 500 cigarettes. The identification of benzpyrene was accomplished by spectrographic techniques and has not been confirmed by chemical analysis. Chemists in this country have generally agreed that their studies indicate that if benspyrene is present in smoke tars, it is less than one part per five million. It is unlikely that this concentration of benzpyrene would be a significant factor in carcinogenesis.

The recent isolation and identification of many interesting compounds from tobacco by chemists in this country and Canada have not yet been formally reported.

The most disconcerting aspect of the chemical work being done is the lack of a good biologic method of testing the various fractions and compounds for carcinogenicity. At present, no one has been able to demonstrate techniques superior to skin painting of mice. This involves a delay of about one year before definitive results can be expected. A further difficulty is the possibility that a carcinogenic effect can only be obtained by the proper balance of several compounds acting synergistically. In this laboratory many of these suggested techniques have been attempted and a brief review of the advantages and disadvantages of each method will be pointed out.

Whole cigarette smoke tar has been produced by a smoking machine patterned after that of Bradford, Harlan, and Hanmer.[3] With this apparatus, approximately 9 Gm. of tar are obtained from each carton of cigarettes. The tar is then dissolved in acetone and 0.2 ml. is applied to the dorsal skin of mice three times weekly. In our studies, in the only group of mice which have reached the cancer age, there is one confirmed carcinoma out of 8 mice (Fig. 1). Other mice have papillomas and some probably will develop cancers in a few months. The disadvantages of this technique are the early death rates from nicotine poisoning (which can be obviated by using graduated doses for several weeks), general toxicity including weight loss, and the long latent period which approximates one year.

The most significant experiment reported to date using whole tar painting is that reported by Wynder, Graham, and Croninger[24] who used 40 mg. of tar in an acetone solution three times a week. Of 81 CAF_1 mice, 59 developed papillomas and 44 per cent developed carcinomas of the skin. The first carcinoma was observed in the forty-second week and the average time of appearance was seventy-one weeks. Control mice painted with acetone developed no tumors. Wynder has indicated that tar with the nicotine removed had equal carcinogenicity.

The possibility that tobacco products may be acting synergistically with other environmental factors is very difficult to study in the laboratory. To date, no data are available indicating the advantage of applying carcinogenic agents simultaneously with tobacco tars. While such experiments could be valuable in indicating whether or not the tobacco fractions are "promoting agents," they must be very carefully interpreted. It is well known that many stimuli give rise to tumors in mice when administered after a polycyclic carcinogen such as 9-10-dimethylbenzenthracene. On the other hand, some polycyclic compounds inhibit the carcinogenic action of others, while in some cases, increase of activity is reported. Wynder and his colleagues have followed administration of crude tobacco tar with croton oil with no increase in tumor incidence. In this regard, it must be borne in mind that human beings are constantly exposed to low levels of atmospheric carcinogens and to low levels of ionizing radiation. The interrelationship of these factors with smoking should be explored.

Preliminary irradiation of the skin has been suggested as a method of preparing the animal skin for painting experiments but no results have been reported.

Ingestion Experiments.—The importance of strain differences should be mentioned since, as it is well known, the susceptibility of different strains of mice to a carcinogen may vary greatly. Swiss mice are felt to be quite susceptible to tobacco tar by Wynder[25] and ourselves. In this Institute, the grown hamster was used to simulate tobacco chewing since it has an oral pouch in which pellets of tobacco mixtures can be planted. These experiments have not been successful. No precancerous changes have been noted when tobacco concentrations were used at the limit of local toxicity.

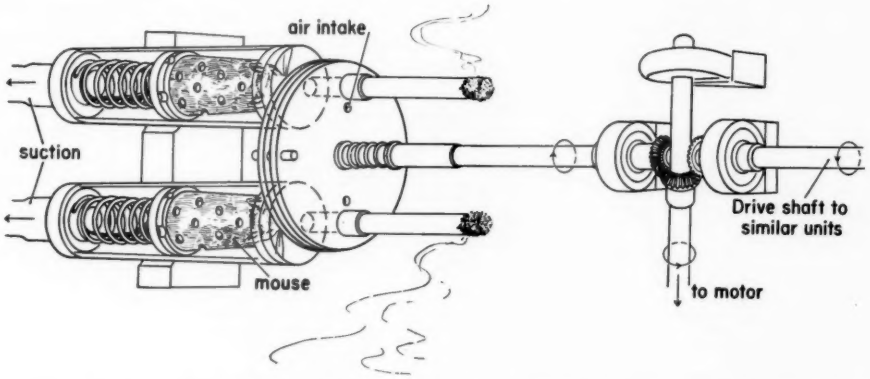
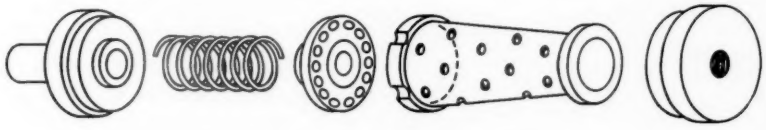
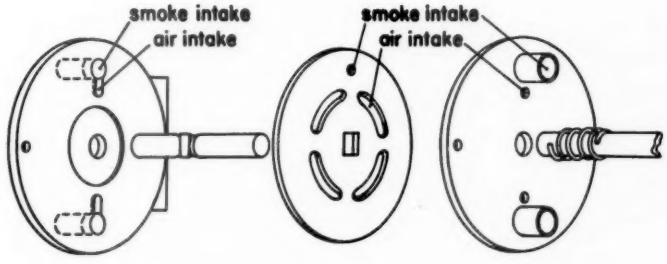


Fig. 2.—Mouse smoking apparatus (top view). Intermittent suction provides a 2-second puff of smoke once a minute followed by clearing of the chamber in a few seconds. The distance between the end of the cigarette and the animal's nose is about 2.5 cm.



DETAIL OF LUCITE CHAMBER



DETAIL OF VALVE
(TOP VIEW)

Fig. 3.—These "exploded" views of a smoking chamber depict the inner chamber which maintains the mouse in the proper position and the rotating valve which regulates the length of the smoke puff and the interval between puffs.

Mice of various strains have been placed on tobacco food mixtures and at ten months no significant changes have been noted. There is a striking difference in toxicity between rats and mice; mice tolerate a food to tobacco ratio

of 25 to 1, rats, 12 to 1. Experiments in which mice have been placed on a mixture of a vitamin-deficient diet and tobacco have been initiated but have not been going on long enough to be significant.

The only recent positive report of similar experiments is that of Holsti and Ermala[11] who reported the presence of papillary carcinoma of the urinary bladder in 15 per cent of the animals surviving one year whose oral cavity and lips had been painted with tobacco tar for 140 consecutive days. Benign papillomas occurred in 87.5 per cent of these animals.

Inhalation experiments.—Several groups have reported experiments in which tobacco smoke was blown into a large chamber containing mice with varying results. Lorenz[16] reported that exposure of strain A mice to tobacco smoke for several hours each day for 28 to 250 days resulted in no increase of lung tumors over control animals. Essenberg[7] exposed strain A mice in a similar chamber for twelve hours each day. At the end of twelve months, a study of 55 mice whose tissues were well preserved revealed an incidence of lung tumors of 91.3 per cent in the experimental animals and 59.4 per cent in the control animals.

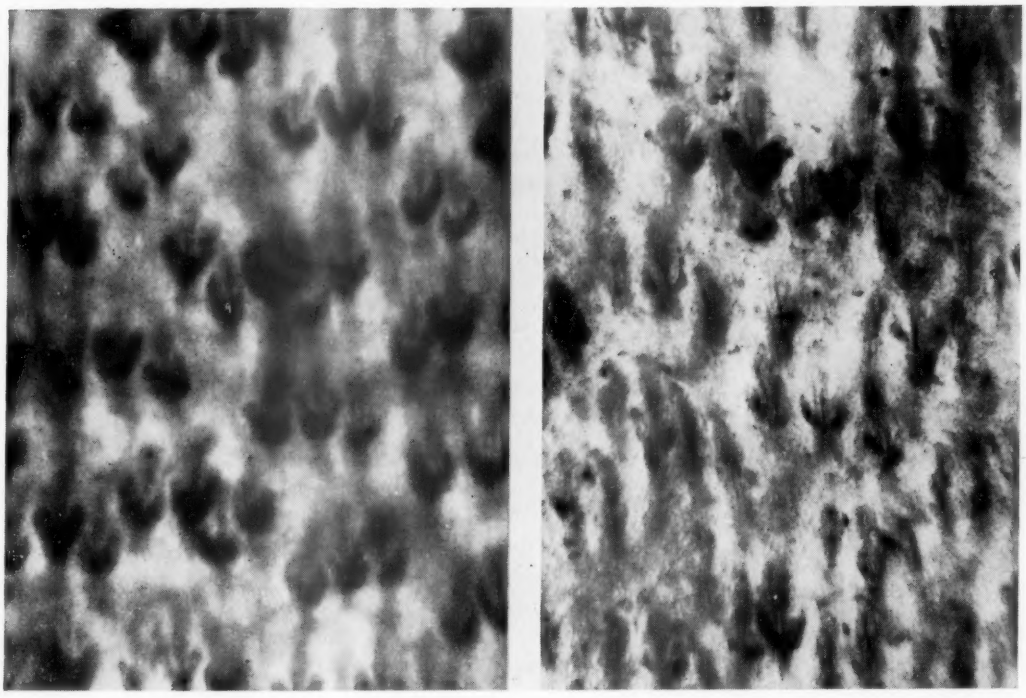
The disadvantage of using a chamber containing many animals is that the large smoke particles settle out before they can be inhaled by the mice and the finest particles remain suspended in the air and are drawn out of the chamber. In order to overcome these objections, attempts have been made to design an individual mouse smoking apparatus so that the mouse is exposed to the main stream smoke as close as possible to the butt of the cigarette.[18] The design presently being used is shown in Figs. 2 and 3. One immediately apparent disadvantage of this apparatus is that the smoke is inhaled through the nostrils of the animal, and the effect of stress associated with their being placed in a confining chamber and exposed to puffs of smoke cannot be perfectly controlled even by exposing mice for similar lengths of time in the chambers. At present, mice are daily being exposed to the smoke of regular commercial cigarettes and those with a low nicotine content.

Sebaceous Gland Studies.—Several investigators have suggested that the disappearance of sebaceous glands in animals painted with various compounds can be used to screen for carcinogenicity. This technique has been used by Suntzeff, who noted the disappearance of sebaceous glands in 100 per cent of their animals painted with a whole tar-acetone solution. This biologic test has been carefully studied in this laboratory to evaluate its use for detecting activity in various tobacco fractions.

Early effects of cigarette smoke condensate upon mouse skin closely resemble those of known polycyclic carcinogens in that the sebaceous glands are destroyed in four to six days. The disappearance of these glands after three or four applications of tobacco tar is striking. (Fig. 4, *A* and *B*).

It has been reported that mice whose skin is in the "resting phase" of hair growth give consistent results with known carcinogens. These observations have been confirmed by our studies. We have extended the examination of test materials by use of a serial dilution technique so that a comparison of the relative potency of various smoke fractions with pure chemical compounds can be made.

On the basis of screening results of a large number of compounds which will be reported elsewhere, it seems likely that positive destruction of sebaceous glands is generally associated with complex polycyclic hydrocarbons including all of the polycyclic carcinogens thus far investigated. There is a rough parallel between activity against sebaceous glands and reported carcinogenic activity. On the other hand, most nonpolycyclic carcinogens which have been studied to date have failed to show similar activity against the glands.



A. *B.*

Fig. 4.—*A*, Whole skin mount stained with p.03 per cent Nile blue to show normal distribution of sebaceous glands. *B*, Whole skin mount depicting the disappearance of sebaceous glands subsequent to three paintings with a smoke tar fraction.

With this procedure as a guide, cigarette smoke condensate has been fractionated with the aim of isolation of pure materials responsible for the sebaceous gland effect. The results to date indicate that the active agent is a lipid which, in the concentrations involved, is soluble in acetone, and is probably a polycyclic hydrocarbon. Crude cigarette smoke condensate has an activity approaching 8 units of biologic activity per gram. One active fraction has an activity of 140 units per gram. For reference, the active polycyclic hydrocarbons, such as benzpyrene, have values above 1,000 units per gram.

SUMMARY

In this paper, many of the controversial aspects of the tobacco-lung cancer problem have not been reviewed, since the primary objective was to summarize various investigative techniques in the human and in the experimental laboratory which should be employed to elucidate further this problem. Unfortu-

nately, even the best designed studies have not given a definite answer free from criticisms of bias, qualifications, and pertinent to the human problem.

The need for additional epidemiological data, more effective biologic tests, and more complete chemical identification of the constituents of tobacco has been indicated.

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THE MECONIUM PLUG SYNDROME

H. WILLIAM CLATWORTHY, JR., M.D.,* WILLIAM H. R. HOWARD, M.D.,**
AND JAMES LLOYD, M.D.,*** COLUMBUS, OHIO

(From the Departments of Surgery and Radiology of The Columbus Children's Hospital and The Ohio State University College of Medicine)

NEWBORN infants with intestinal obstruction due to the inability of the colon to rid itself of the meconium residue of nine months of fetal life are not uncommon. In such instances, it is presumed that either the meconium mass or the colonic motility is so altered that the normal unplugging process is impeded and deflation of the alimentary tract is retarded. This relatively benign form of obturation obstruction may vary from a mild stasis which can be relieved by the insertion of a thermometer or a finger into the rectum to a complete unrelenting form of mechanical obstruction. Infants who do not respond to anal stimulation rapidly develop the classical signs and symptoms of low intestinal obstruction: abdominal distention with hyperactive intestinal patterning, bile-stained vomiting, and continued obstipation.

During the past five years at The Columbus Children's Hospital, we have had an opportunity to study nine such unrelenting cases. These "plugged-up babies" were sufficiently confusing from the standpoint of their differential diagnosis and surgical management to warrant presentation here.

CLINICAL FEATURES

The significant clinical findings in the nine cases of neonatal intestinal obstruction due to this meconium plug syndrome are summarized in Table I.

Eight of the infants were male, seven were white and two were Negro. The age of the patients at the time of admission varied from one to six days and the birth weights ranged from 4 pounds, 6 ounces, to 8 pounds, 13 ounces, the average weight being 5 pounds, 5 ounces (approximately 1 pound less than normal).

All of the infants had evidence of intestinal obstruction shortly after birth. All developed moderate to severe abdominal distention and seven began to vomit on the first day of life. None of the infants had passed any normal meconium although two gave a history of having evacuated a very small amount of pale mucoid material prior to their admission to the hospital.

The general appearance of the infants was relatively good. Only two showed marked evidence of dehydration, listlessness, and lethargy ordinarily associated with intestinal obstruction. In each instance the abdomen was moderately to markedly distended and there were visible and palpable loops of tense bowel visible through the abdominal wall which frequently arranged themselves in a stepladder pattern characteristic of mechanical low intestinal

*Associate Professor of Surgery (Pediatric), The Ohio State University College of Medicine and Chief of Surgical Service, The Children's Hospital.

**Assistant Professor, Department of Radiology, The Ohio State University College of Medicine and Radiologist, The Children's Hospital.

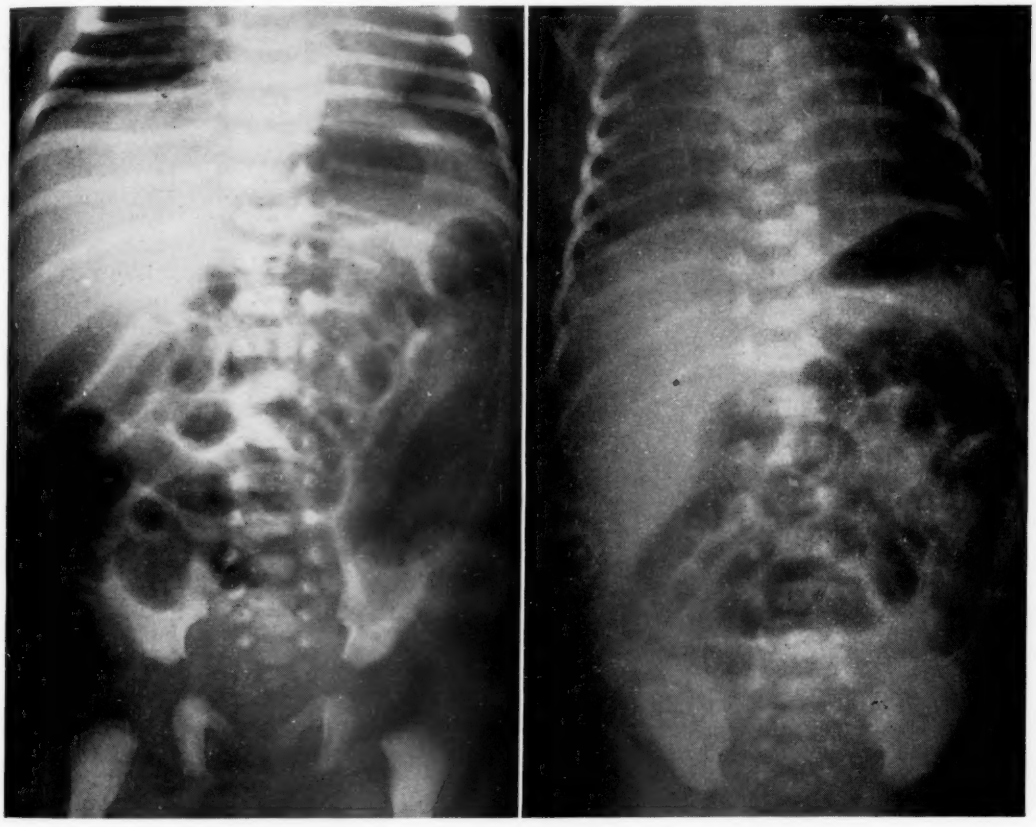
***Former Assistant Resident in Surgery, The Children's Hospital.

TABLE I

NO.	ADMISSION AGE	COMPLAINT	STOOLS	RECTAL EXAMINATION	X-RAY FINDINGS	STOOL TRYPSINS 1:5	STOOL TRYPSINS 1:10	RELIEVED BY	FOLLOW-UP
1	2 days	Vomiting since birth	One small meconium	No meconium	Dilated bowel; no fluid levels; small left colon	+	+	Barium enema	Barium enema normal; asymptomatic; overweight; well 5 years
2	2 days	Vomiting since birth	None	Meconium present	Bowel distention with fluid levels; no barium enema	−	−	Anal dilatation	Well 3 years; chest normal
						+	+		
						+	+		
						+	+		
3	2 days	Vomiting since birth	None	Meconium present	Distended loops; no fluid levels; no barium enema	+	+	Anal dilatation	Well 3 years; chest normal
						+	−		
						+	−		
4	1 day	Increasing distention	None	No meconium	Marked bowel dilatation; no fluid levels; small colon	+	−	Barium enema	Well 3 years
						±	−		
						±	+		
						+	+		
						+	+		
5	6 days	Vomiting since age 2 days	None	No meconium	Bowel obstruction with fluid levels; small colon and dilated cecum	−	−	Biopsy bowel and enterostomy (ganglion cells normal)	Normal progress; 6 months
						−	−		
						±	+		
						+	+		
6	1 day	Increasing distention	None	Meconium present	Dilatation bowel; no fluid levels; small sigmoid colon			Anal dilatation	Well 2 years
7	1 day	Vomiting and distention since birth	None	No meconium	Bowel dilatation; no fluid levels; small left colon	+	+	Biopsy bowel and colostomy; colostomy closed (ganglion cells normal)	Well 2 years
						+	+		
8	3 days	Distention and regurgitation	One small meconium	No meconium	Marked bowel distention; no fluid levels; small left colon	−	−	Peroxide enema	Barium enema normal; chest normal; mentally retarded 15 months
						+	+		
						+	+		
9	3 days	Increasing distention and vomiting	None	No meconium	Distended bowel with fluid levels; small left colon	−	±	Peroxide enema	Well 3 months
						−	−		
						+	+		

obstruction. In several instances, the veins of the abdominal wall were quite prominent. The rectal examination in four of the infants yielded meconium and in each case the child was subsequently relieved of his obstruction without further treatment. In the remaining five infants, no meconium was passed following digital examinations and the rectum was noted to be contracted and empty.

The roentgenologic findings varied with the duration of the obstruction and the site of the meconium impaction but were quite characteristic in the seven cases in which a barium enema was accomplished prior to the relief of the obstruction.

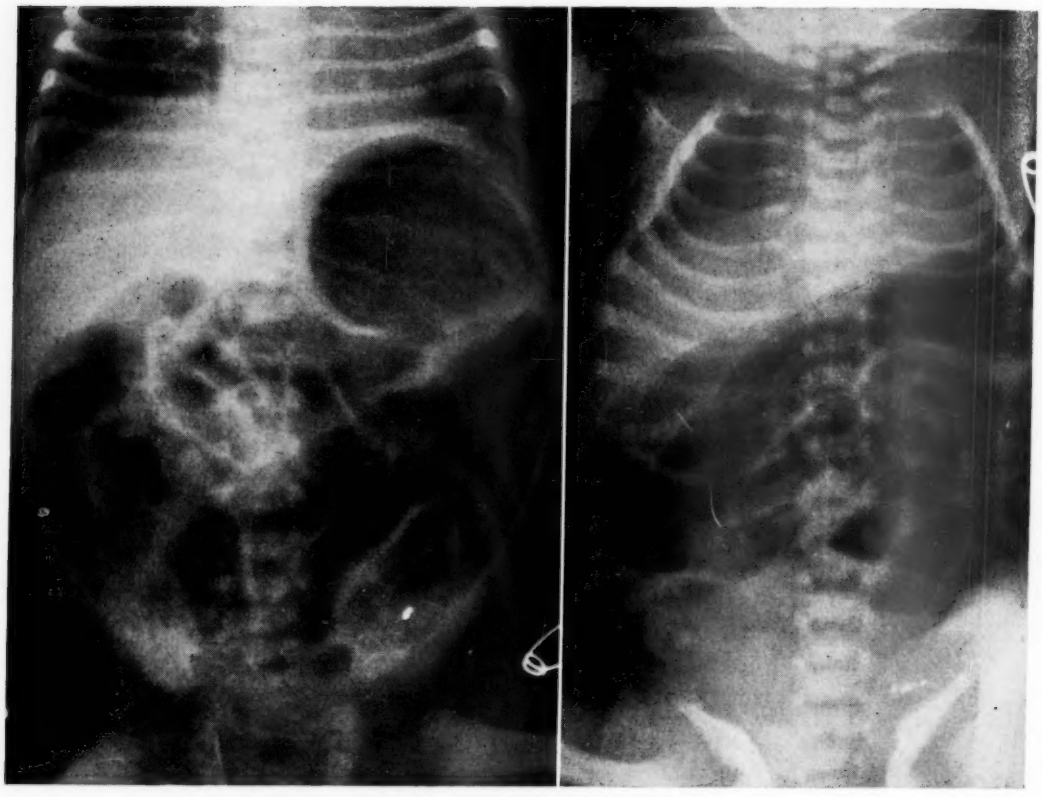


A. *B.*

Fig. 1.—Case 2. A 2-day-old infant with vomiting since birth. Recumbent and upright abdomen films show generalized nonspecific dilatation of bowel with fluid levels. Relieved by rectal examination.

The initial plain and upright films showed a generalized gas pattern with more or less marked dilatation of the entire bowel. Satisfactory differentiation between the large or small bowel was, as usual in this age group, impossible. Fluid levels were present in three cases (Fig. 1, Case 2).

The first barium enema was performed shortly after the wet scout film had been studied. The rectosigmoid and usually the descending colon up to the splenic flexure (in one instance the transverse and, in one instance, the



A. *B.*

C.

Fig. 2.—Case 9. A 3-day-old infant with increasing distention and vomiting. Plain films show marked bowel dilatation with fluid levels, and barium enema reveals ribbonlike rectosigmoid and descending colon with caliber change at splenic flexure. Note meconium plug producing filling defect in distal transverse colon. Relieved by barium and peroxide enemas.

entire colon to the cecum) were narrow and ribbonlike. The thin barium contrast material passed through this small segment without difficulty up to the point of caliber change where the dilated portion of the colon was reached. The point of caliber change (point of obstruction) was either long and tapering or funnellike. The colon proximal to the point of caliber change was usually dilated and after initial hesitation allowed the barium mixture to flow gradually around the meconium mass into the gas-filled bowel. In two instances the terminal ileum filled with barium (Fig. 2, Case 9).

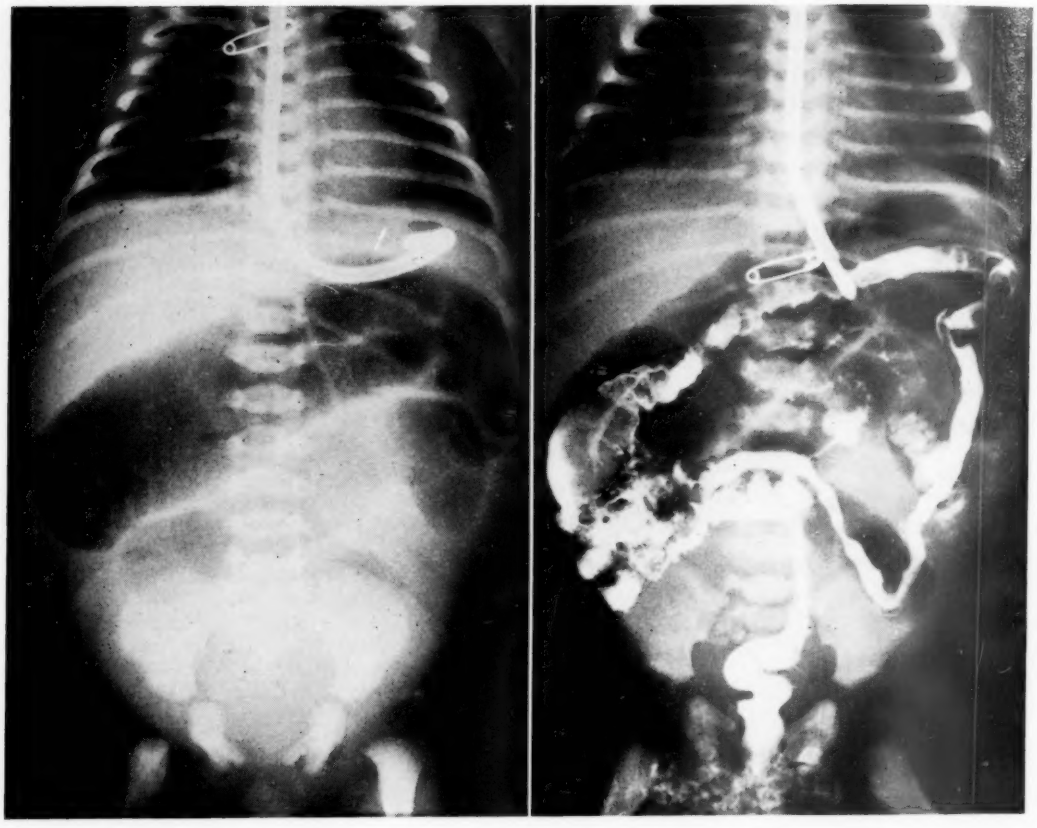
In addition to the routine laboratory procedures, eight of the infants had one or more examinations of the meconium which was subsequently passed or obtained at operation. Each meconium sample was examined for the presence of trypsin by the Johnstone[1] modification of the Shwachman[2] gelatin film test controlled with trypsin inhibitor. In six infants, serial examinations were done at daily intervals. In each such instance, when the *first* meconium was obtained, there was no tryptic activity in the 1:5 and 1:10 dilutions. Subsequently, the meconium from the same infants showed a progressive increase in tryptic activity. All of the infants' stool trypsins were positive by the time they left the hospital.

TREATMENT

Four infants responded to digital examination with the passage of first thick and then more fluid meconium and recovered rapidly and completely from their obstructive symptoms. In two instances the relief of obstruction followed the barium enemas at which time a firm mass of meconium was passed. Two additional patients, who were not relieved of their obstruction by digital examination or by repeat barium enemas, were given dilute hydrogen peroxide enemas (one part 3 per cent hydrogen peroxide to three parts normal saline solution) as recommended by Olim and Cuiti.[3] In each instance the peroxide enema was followed immediately by the passage of large amounts of thick meconium and gas. The remaining two cases warrant a discussion in some detail since a clinical and radiographic diagnosis of congenital aganglionic megacolon was made and an ileostomy or colostomy was performed.

CASE 5.—This infant was 6 days old at the time of admission with a history of having vomited since the second day of life. The birth weight was 8 pounds, 13 ounces. Physical examination revealed a somewhat dehydrated infant with a shiny distended abdomen on which intestinal patterning was evident. The rectum was contracted and empty. Plain films of the abdomen were consistent with a complete low intestinal obstruction. Barium enema flowed freely into a small and ribbonlike colon until the cecum was reached, at which point the barium column ballooned out into a gas- and meconium-filled segment. A small amount of the contrast material refluxed into the widely dilated ileum (Fig. 3).

The infant was presumed to have a congenital aganglionic colon, and following preoperative preparation a laparotomy was carried out through a right rectus incision. Upon opening the peritoneum, there was a moderate amount of clear fluid and several dilated loops of ileum presented. No point of mechanical obstruction was found. The appendix was removed and biopsies of the bowel wall were taken which subsequently showed normal ganglion cell distribution. A Weitzel type enterostomy was performed in the terminal ileum.



A. *B.*

Fig. 3.—Case 5. A 6-day-old infant with distention and obstipation. Plain films show gross dilatation of bowel and barium enema reveals ribbonlike colon with dilated cecum containing large filling defect (meconium plug).

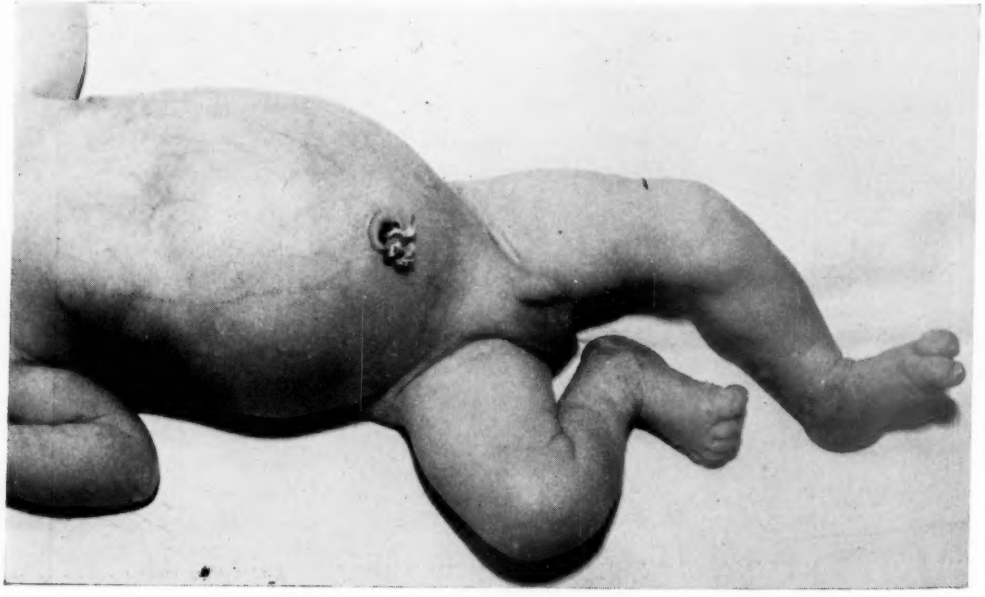
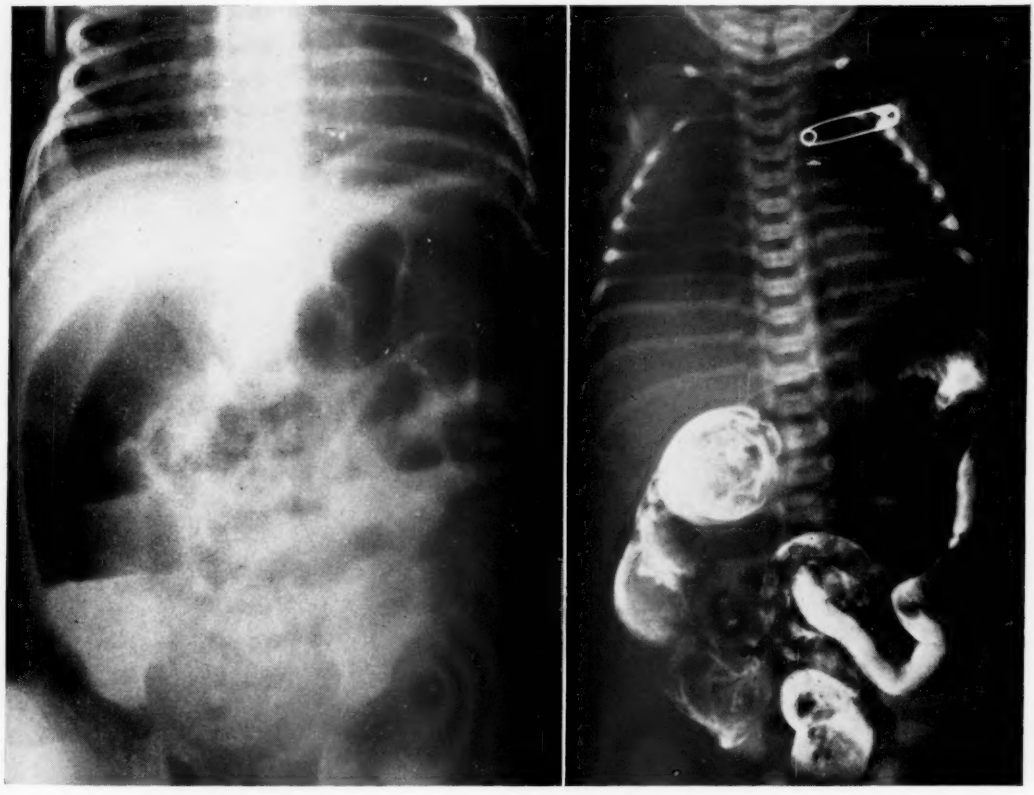


Fig. 4.—Case 7. A 1-day-old infant with vomiting, distention, and obstipation. Note degree of distention and dilated abdominal wall veins typical of the meconium plug syndrome.

The child decompressed rapidly and on the fourth postoperative day had spontaneous bowel movements. The enterostomy tube ceased to drain and was removed on the eighth postoperative day. Gelatin film trypsin studies were positive on the duodenal juice; negative initially, and weakly positive thereafter on the stool.

The child was discharged from the hospital on the twenty-fourth postoperative day and followed in the Surgical Clinic for nine months. He developed no symptoms of gastrointestinal or respiratory dysfunction.

CASE 7.—A 1-day-old white, 5 pound, 13 ounce, male infant was admitted to the hospital because of vomiting of bile-stained material, abdominal distention, and failure to pass meconium. Physical examination revealed a markedly distended infant with dilated abdominal wall veins and visible peristalsis over which high-pitched borborygmus was present (Fig. 4). The rectum was contracted and contained no meconium. Recumbent and upright films of the abdomen showed a nonspecific dilatation of the bowel with fluid levels. Barium enema studies of the colon showed the rectosigmoid and descending colon up to the splenic flexure to be contracted. At the splenic flexure there was an S-shaped curve and a sharp differential caliber change with a dilatation of the transverse ascending colon and cecum (Fig. 5).

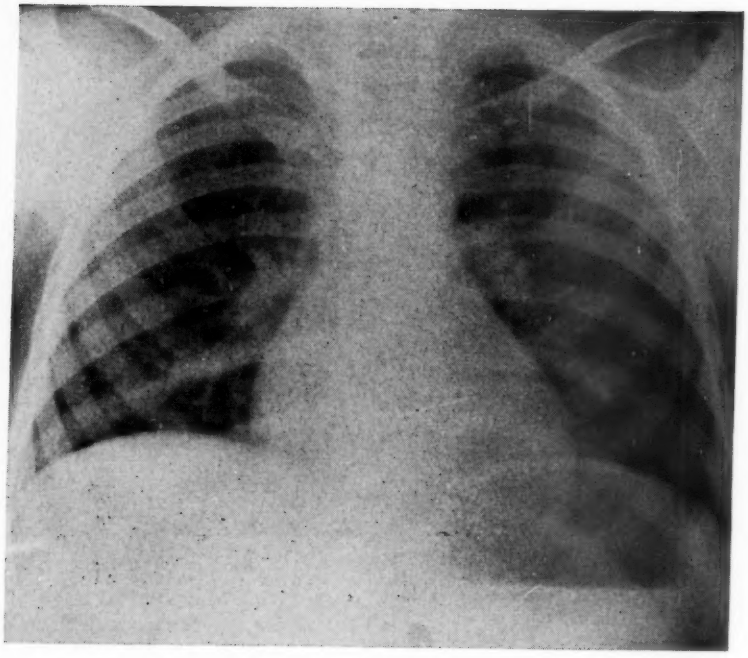


A. *B.*

Fig. 5.—Case 7. Upright film of abodmen shows severe generalized dilatation of bowel with fluid levels. The barium enema demonstrates a small left colon and abrupt caliber change at splenic flexure.

A diagnosis of Hirschsprung's disease of the left colon was made, and, at operation through a left transverse rectus incision, the transverse colon was found to be hugely distended and thickened. Attempts at decompression with a No. 13 needle were unsatisfactory because of the thickness of the meconium. A left transverse colostomy was performed. The following day when the colostomy was opened, a biopsy of the bowel wall was obtained which showed a normal complement of ganglion cells.

A.



B.

Fig. 6.—Case 7. Barium enema six months after colostomy closure showing normal caliber of colon throughout and no evidence of Hirschsprung's disease. The chest film is normal.

The child was completely relieved by his colostomy and was discharged from the hospital on the twelfth postoperative day.

One year later the child returned to the hospital for a Swenson pull-through procedure. However, at the time of operation, a biopsy of a generous portion of the left colon which had previously been described as contracted and ribbonlike showed a normal complement of ganglion cells. For this reason, the colostomy was taken down and an end-to-end anastomosis carried out without resection of the left colon. A proximal tube colostomy was used for temporary decompression. The child had his first stool by rectum on the fourth postoperative day and was discharged on the fourteenth day.

Subsequent follow-up studies including barium enema and chest film indicate that this child has no gastrointestinal dysfunction or evidence of pancreatic insufficiency (Figs. 6 and 7).

Fig. 7.—Case 7. At age 2 years, weighing 29 pounds.

FOLLOW-UP

This group of nine patients has now been followed in the Surgical Clinic or with the family physician for from three months to five years. All have remained essentially well. None have shown any evidence of fibrocystic disease clinically since all have enjoyed normal growth and development on a regular

diet, and freedom from respiratory infections. Recent chest roentgenograms of Cases 2, 3, and 7 showed no evidence of pulmonary involvement characteristic of fibrocystic disease.

None of these children has experienced any difficulty with constipation, obstipation, intermittent abdominal distention, or colic such as would characterize a congenital type of megacolon. In three cases, repeat barium enemas (after relief of the obstruction) have shown the colon to be normal in size and in function.

DISCUSSION

It is evident from a study of these nine cases of intestinal obstruction presumably due to the presence of a meconium plug that we are not dealing with infants who have "meconium ileus" associated with pancreatic fibrosis such as has been described by Forrer,[4] Landsteiner,[5] Bullowa and Brennan,[6] Andersen,[7] and Farber.[8] Nor do these infants, once relieved of their obstruction, show any semblance of chronic intestinal dysfunction similar to that commonly associated with a segmental absence of the ganglion cells of the myenteric plexus (Hirschsprung's disease) such as described by Tiffin, Chandler, and Faber,[9] Zuelzer and Wilson,[10] Swenson, Rheinlander, and Diamond,[11] Bodian, Stephens, and Ward,[12] and Hiatt.[13]

Although the genesis of the meconium plug syndrome is not yet entirely clear, it is our feeling that it is probably due to an alteration in the character of the most distal portion of the meconium mass. This may be related to a deficiency in its trypsin content which Farber has demonstrated as being so important to the process of liquification of normal meconium. The fact that none of the first meconium evacuated by the infants in this series of cases possessed tryptic activity even in the 1:5 and 1:10 dilutions would support this view and perhaps provide the most acceptable theory for the genesis of this not uncommon condition in newborn infants.

Radiographically, the presence of a small left colon may readily be confused with true Hirschsprung's disease. Swenson[14] has recently emphasized the fact that congenital megacolon in the newborn may be indistinguishable clinically and radiographically (on the plain films) from small intestinal obstruction. For this reason, he feels that no infant with low mechanical obstruction should be subjected to an abdominal operation until a barium enema has been performed.

Our experience would certainly bear out this fundamental contention, but in addition, it would appear that it would also be necessary to remember that true megacolon may in certain instances be readily confused with the meconium plug syndrome if at the time of the barium enema the radiologist considers the presence of the collapsed distal colon pathognomonic of aganglionic disease.

Differentiation by barium enema between the meconium plug syndrome and Hirschsprung's disease may be impossible on a single examination; however, by repeating the barium enema twelve or twenty-four hours later, it has been observed that in these cases of meconium plug syndrome there is a

decided increase in caliber of the distal, previously ribbonlike colon and that there may be migration downward of the point of caliber change. Neither of these radiographic findings have been noted in true Hirschsprung's disease in which the area of narrowing is generally (though not necessarily) confined to a relatively short rectosigmoid segment.

Fortunately, the infant who is relieved of his meconium plug obstruction does not have a recurrence of obstipation or distention, whereas an infant with true Hirschsprung's disease experiences more or less continuous episodes of intermittent colonic obstruction.

CONCLUSIONS

Newborn infants with low intestinal obstruction may present physicians, radiologists, and surgeons with a confusing diagnostic problem. Abdominal distention, bile-stained vomiting, and a failure to evacuate meconium are characteristic of obstructions from mid-ileum to the anus in this age group. Radiographic studies while frequently pathognomonic of mechanical obstruction rarely enable one to differentiate between large or small bowel or to determine the exact nature of the obstructing mechanism. In spite of these difficulties, some authors[15-17] have recently recommended surgical intervention of an exploratory nature once a clinical and radiographic diagnosis of intestinal obstruction has been established. Unfortunately, such a course of action may lead to an unproductive surgical procedure at which time the alimentary tract is found to be in continuity with no definite point of obstruction. Such a situation is most likely to arise in instances of colonic obstruction due to Hirschsprung's disease or to the meconium plug syndrome.[18]

We have described a series of cases of colonic obstruction occurring in the neonatal period which apparently is due to inspissated meconium and which is clinically and radiologically readily confused with other forms of high-grade mechanical obstruction in the lower intestine. Barium enema studies, which should be carried out on every such infant, are quite characteristic. The left colon is long, smooth, ribbonlike and blooms into a dilated proximal segment usually in the region of the splenic flexure. In such infants, early surgical exploration definitely is not indicated since relief of the obstruction can be more simply achieved by a judicious rectal examination or, when this fails, by carefully repeated barium or hydrogen peroxide enemas. None of these patients has developed pancreatic fibrosis or congenital megacolon.

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PNEUMOPERITONEUM IN THE MANAGEMENT OF GIANT HERNIA

EDWARD E. MASON, M.D., PH.D.,* IOWA CITY, IOWA

(From the Department of Surgery, State University of Iowa College of Medicine)

INTRODUCTION

THE use of pneumoperitoneum to stretch the abdominal wall to facilitate repair of giant hernias is an accepted and common procedure in most South American surgical centers. The authors' attention was first directed toward this procedure by an Argentine surgeon, George Reales, in 1951. Moreno[1] is credited with first use of the method in May, 1940. He reported his experience in this JOURNAL in 1947. The only other report in United States literature, and the only report by a surgeon in this country, was that of Koontz[2] describing its application in four patients. He used large sheets of tantalum mesh to close defects that could not be closed with normal tissues or to reinforce the repair. In one of these patients the total amount of air injected was only 1,700 ml. over a period of ten days; in another patient the total duration of pneumoperitoneum was only five days. Koontz mentions in a footnote that additional patients had been treated. The fact that a proponent of tantalum mesh repair found pneumoperitoneum of use serves to call attention to the place of this procedure in the treatment of large hernias. As illustrated in Koontz' experience, and also in the present series, reinforcement of the abdominal wall with tantalum mesh or other material is not a substitute for re-establishing abdominal domain. Likewise, the ability to repair a hernia without tension and without a splint does not guarantee that the repair will remain intact if the fascial structures used are inadequate, or if obesity, chronic cough, or other adverse influences persist or recur.

The dearth of reports in this country regarding this technique indicates either a lack of familiarity with it or poor results following its use. This paper will attempt to dispel doubts regarding the value of the method when properly indicated and used, and will also report observations and possible errors of judgment that have been made during its use in the author's initial experience with nine patients.

TECHNIQUE

Under local anesthesia and by use of a blunt needle, air is injected into the free peritoneal cavity at a convenient place well away from any scars of previous surgery. A 50 c.c. syringe fitted with a three-way stopcock is attached to the needle by sterile rubber tubing to prevent motion of the syringe from being transmitted to the needle during injection. Subsequent refills have been given in amounts and at intervals necessary to keep the patient mildly uncomfortable. An arbitrary total time of one month has been used in most cases, but with experience this can be altered to suit the requirements of the individual patient. After the initial injection there is slight shoulder pain for a few days, which may be relieved

*Assistant Professor of Surgery.

TABLE I

CASE NUMBER	AGE (YR.)	SEX	REPAIR DATE	DURATION OF HERNIA (YR.)	ORIGIN OF HERNIA	INITIAL INJECTION (ML.)	TOTAL AIR INJECTED (ML.)	DURATION OF PNEUMO-PERI-TONEUM (DAYS)	COMMENTS
1	50	F	6/19/53	26	Umbilical hernia repair; transverse defect	1,000	13,000	30	Repair attempted 18 years earlier; "inoperable" 11 years earlier; repaired with No. 30 steel wire; reinforced with fascial graft; no recurrence
2	48	F	8/26/53 10/16/53	14	Midline vertical; cesarean section and umbilical hernia repair	1,800	9,300	30	Obesity and poor tissue were underlying problems; emergency excision of large ulcer of sac plus removal of small bowel segment; pneumoperitoneum during recovery and staged repair; recurrence with weight gain
3	61	M	8/12/53	48 8/12	Right paramedian; gastrectomy with postoperative dehiscence	3,000	12,500	34	Poor risk because of arteriosclerotic heart disease; no recurrence
4	63	M	11/25/53	18	Right paramedian; exploration of gall bladder and appendectomy; asthma; postoperative, dehiscence due to cough	4,000	9,000	45	Inadequate stretching; should have had a staged repair and more intensive pneumoperitoneum; greatly improved but small defect remains in upper portion of wound
5	51	M	5/ 4/54	?	Recurrent indirect inguinal; unable to give history; inmate of mental institution 40 years	1,000	10,000	30	Ascending colon and small bowel found in sac; orchiectomy; all layers sutured to Cooper's ligament; no recurrence

6	52	F	9/30/54	5	Vertical midline; tubal pregnancy and repair umbilical hernia; gradual appearance and increase in size of hernia	4,500	18,500	54	One of largest in group; repair easy and edges of defect could be overlapped; had diabetes, and heart disease requiring digitalis and diuretics; no complications from surgery; no recurrence
7	69	F	10/26/54	9/12	Right paramedian; exploration for gastrointestinal bleeding; postoperative evisceration closed with skin	400	2,800	28	No real hernia but a large defect and was a poor risk because of heart disease; no recurrence
8	58	M	12/ 9/54	?	Indirect inguinal; inmate of mental institution; no history	1,000	9,000	25	Developed subcutaneous wound infection postoperatively which responded to opening skin wound; no recurrence
9	66	M	2/16/55	15/12	Right paramedian; appendectomy; postoperative wound infection and evisceration	1,500	10,100	36	Secure repair obtained with overlapping edges of wound; no recurrence

by recumbency. If rapid distention with air is done initially, upper abdominal pain results which is probably due to the stretching of the liver attachments to the diaphragm. Roentgenograms taken in the upright position demonstrate how the suspensory ligaments support the liver after pneumonperitoneum since the dome of the liver is no longer held up tightly by the suction effect. It is unlikely that air directly irritates the diaphragmatic peritoneum by contact. The resulting poorly localized upper abdominal pain and sharper shoulder pain are well known to those physicians who have used pneumoperitoneum in the treatment of tuberculosis. In the patient with a large hernia, adhesions, and so forth, these abdominal pains may at times offer a problem in differential diagnoses, especially if the patient has also had bouts of partial intestinal obstruction. In the present series, some of the patients have been kept under close observation in the hospital and the pneumoperitoneum refills postponed for a few days or a week while these initial pains subsided. Intra-abdominal complications have been watched for by observing for signs of peritoneal irritation, borborygmi, elevated temperature, leukocytosis, and so forth. There has been no indication that any complication has occurred in any of these patients. It has not been necessary to remove air, but this could be used as an additional means of differentiating stretch pains from signs of complicating intra-abdominal disease.

One potential objection to the method is that it may utilize a bed for a longer time, greatly increasing the total cost of care. It has been necessary to hospitalize most of these patients only until they were over the acute symptoms resulting from the pneumoperitoneum. They were then followed as outpatients, refills being performed as needed, until time for the repair. After the first few days most patients are able to return to normal daily activity.

Crossed and overlapped strips of adhesive plaster are used to compress the hernia to force the air intra-abdominally. The skin is protected with tincture of benzoin and the tapes are extended well out onto the lower chest, flank, and thigh. When a satisfactory corset is available, it is used instead of or, more commonly, in addition to tape. At the time of refill the portions of tape that are loose are cut away, and fresh tape strips are used to tighten the dressing. With some extremely large hernias refills may be less frequent and the increased intra-abdominal tension can be obtained by simply forcing more of the air out of the sac into the abdomen by increasing the tightness or compression of the tape dressing or corset. Usually the interval between refills is five to seven days.

DISCUSSION OF CASES

The nature of the problem in each of the nine cases is outlined in Table I together with some of the more important information regarding treatment. The patients are listed chronologically as they were seen. Three of the patients will be discussed in detail to illustrate certain points that will be made regarding our experience with the technique.

CASE REPORTS

The first patient is typical of those whose giant hernias have in the past been considered inoperable by well-qualified surgeons. The herniation followed repair of an umbilical hernia and an appendectomy that was performed twenty-six years earlier. One unsuccessful attempt at repair had been made eighteen years prior to admission. Eleven years prior to entrance the patient was first seen in our outpatient department, at which time the examiners decided that most of the abdominal viscera were probably in the hernia sac and that it would be impossible to replace them within the abdominal cavity. The corset prescribed supported the hernia adequately, but the patient had increasing difficulty with constipation, abdominal distress, and bouts of nausea and vomiting. On two occasions, two years before and again two months before admission, hospitalization had been required for treatment of bowel obstruction. In both instances nonoperative treatment had been successful in relieving the obstruction. As a result of the bouts of partial bowel obstruction the patient had undergone a recent weight loss of 30 pounds, but she still appeared moderately obese, weighing 171

pounds. There were three defects in the transverse mid-abdominal incision and most of the bowel seemed to be out in the hernia sac. After keeping the patient mildly uncomfortable with pneumoperitoneum for a month sufficient room was available within the abdominal cavity for the contents to be easily replaced. A secure repair was obtained with normal tension on the wound edges.

It is difficult to judge exactly how much increase in abdominal cavity size is being obtained by the use of pneumoperitoneum. It is common at the time of repair to find more room available than is needed, and the edges of the wound can frequently be overlapped to give a more secure repair. An excess of room is no problem except that, if the tissues are poor, excessive and rapid stretching might further weaken them. A more serious error is to underestimate the amount of room obtained with pneumoperitoneum, as occurred in the fourth patient. This patient was an overweight, asthmatic, emphysematous truck driver who had made no serious effort to stay on a weight reduction diet and whose hernia was aggravated by coughing spells during which he frequently broke the lacings on his corset. The defect had been present since an emergency exploration of the gall bladder and performance of an appendectomy through a long right paramedian incision twenty years before.

Several injudicious decisions were made in the handling of this patient. In addition to accepting this patient's failure to cooperate in weight reduction, compromise was made on the intensity and frequency of refills in order that the patient could remain at his job. At operation, insufficient room was available. The omentum and mesenteries were extremely fat and it was thought that sufficient room might be obtained by resection of the omentum and the right colon. This was done making a closed end-to-end anastomosis between ileum and transverse colon, but a defect in the upper end of the incision still remained that could not be approximated. This was closed with a fascial graft removed from the right thigh. It was necessary to excise over 800 square centimeters of redundant skin and sac.

Postoperatively the patient developed diarrhea and a brief period of hypovolemia, hemoconcentration, and metabolic acidosis, all of which responded to appropriate fluids and discontinuation of antibiotics. The tissues healed poorly and separation of the skin edges and part of the grafted area occurred. In time the wound healed but the result was less than the complete repair that had been the original goal. The patient is now satisfied with the much smaller defect and declines further surgery. He has maintained a lower body weight that was an unintentional by-product of our vigorous therapy. This may assist in maintaining the remaining defect at its present small size.

This patient would have been better off if the operation had been simplified and the repair partially postponed. No need existed to excise bowel and omentum in order to gain room, as is evidenced by the fact that there was still insufficient relaxation of the abdominal wall to allow approximation of the edges of the defect. The lower half of the defect was closed easily with No. 30 steel wire placed in very tough, thick wound edges. This portion of the wound has remained secure. The upper portion of the sac should have been left for decompression until further stretching had been secured by resumption of pneumoperitoneum. This patient was a victim of the "all-or-none" philosophy which has been too commonly applied to large hernias and about which more will be stated later.

The second patient that was treated illustrates the use of pneumoperitoneum during the staged repair of a giant hernia, initially operated upon under semiemergency circumstances. Fourteen years before admission this patient had a cesarean section and a simultaneous attempt at repair of an umbilical hernia. An incisional hernia began to appear one year later. Two unsuccessful attempts had been made to repair the defect, thirteen and seven years, respectively, prior to admission. Three months before entrance she was seen at University Hospital weighing 253 pounds, complaining of occasional attacks of vomiting, and with the hernia hanging down to mid-thigh region. She was given a diet and asked to lose at least 100 pounds as her part of the preparation. During the next three months she did lose 20 pounds chiefly because she was unable to eat part of the time. One month before admission the patient's ankles became swollen and she developed tachycardia, orthopnea, and dyspnea. These symptoms and signs improved after institution of a low salt diet and digitoxin. Ten days before entrance she was hospitalized near her home with an area of tender-

ness situated over the most dependent part of the hernia. A large, hot, red mass developed at this point with associated nausea, vomiting, chills and fever. The area broke down, draining a large amount of purulent material and leaving an ulcer 8 cm. in diameter. The base of the ulcer was formed by a dilated loop of small bowel covered with a dirty greenish exudate. The edges were undermined and the surrounding skin was thick and edematous. There was, however, no evidence of intestinal fistula. When the patient was supine, the hernia hung down over her thighs and kinked the contained bowel enough to account at least partially for the intestinal obstruction that was present. When the sac was elevated there resulted a large emesis of feculant material. Fortunately the patient was awake and therefore did not aspirate any of this.

The initial treatment lasted three days and consisted of general and local cleansing, elevation of the hernia by means of wide adhesive plaster which was applied from near the axilla, along the chest wall, around the hernia and back along the opposite side to the opposite axilla. This, plus slight Trendelenberg position, elevated the sac and partially relieved the intestinal obstruction. A long intestinal tube was passed to accomplish further decompression and an indwelling gastric tube was used to prevent any further vomiting.

As soon as the bowel was decompressed and the patient's fluid and electrolyte balance was satisfactory, the first stage of the repair was undertaken. The skin around the ulcer was carefully cleansed and the ulcer was closed by incising the skin around the ulcer and approximating the cut edges. A formal operative procedure was then carried out consisting of the removal of a segment of small bowel along with the ulcer and an end-to-end anastomosis utilizing Wangensteen clamps with a single row of 4-0 silk Lembert sutures. The edges of the fascial ring were completely delineated and all adhesions divided. The lower one-third of the defect was repaired, using No. 30 stainless steel wire to approximate the edges of the wound, which were composed of very thick, tough, fibrous tissue. It was quite evident the remaining defect was needed for decompression since some of the viscera could not have been forced into the abdominal cavity at this time. Fine nonabsorbable suture material was used to close the remaining hernia sac and the overlying skin. The area was reinforced with adhesive plaster while the patient was still under anesthesia. Penrose drains were used along the skin closure to prevent the adhesive plaster from sticking and to allow any serum to seep to the ends of the wound rather than to soak and loosen the adhesive plaster. During this operation 500 ml. of blood, 500 ml. of saline solution, and 500 ml. of dextran were administered. In spite of this, the pulse rose from 90 to 110 and the blood pressure fell from 100/80 to 90/70 during the three-hour procedure. The operation would have been terminated without repairing even the lower part of the defect if the patient's general condition had seemed to require this. Postoperatively there were no signs of disturbed circulation or interference with respiration. When the wound was dressed on the sixth postoperative day it was noted that the remaining sac was still large enough to completely overlap the lower end of the incision and the pubis.

Ten days after this semiemergency procedure the wound appeared to be healing well and pneumoperitoneum was therefore initiated with 1,800 ml. of air. The hernia was protected with continued crossed adhesive plaster. By the nineteenth postoperative day the patient had regained her strength, was ambulatory, and helping to serve trays and do other work about the ward. Pneumoperitoneum was then continued on an outpatient basis until time for the second operation five weeks after the first stage procedure. The remaining defect was then closed without tension and with adequate room for all of the viscera.

This patient also serves to illustrate the need for solving underlying problems such as obesity and poor tissues which are not only responsible for the extreme size of some incisional hernia but may also contribute to recurrence of the hernia after it has been repaired. The fascial structures were poor and although it was possible actually to overlap the edges to reinforce the repair, there were weak areas discernible in the surrounding abdominal wall at a distance laterally. The tissues had an edematous appearance which suggested that a longer interval might have been desirable between stages. The immediate convalescence was satisfactory. The patient was enthusiastic about the "new life" before her and expressed complete willingness to follow a low calorie diet. The patient's underlying problem

soon became evident, however. During the next eighteen months she gained 80 pounds, repeatedly assured her physicians that she was limiting her diet to the prescribed 1,000 calories a day, and demonstrated other stigmata of an immature and inadequate personality. The hernia recurred and gradually grew in size as the patient's weight increased.

In the hope of forestalling a seemingly inevitable progression toward repetition of the previous train of events, an elective operation was carried out through the hernia sac in which the proximal two-thirds of small bowel was sidetracked from the food stream, as described by Kremen.[3] During the fourteen months since this latter procedure the patient's weight has remained at 265 pounds. Additional small bowel will need to be diverted if this is to be of any value in this patient.

The seventh patient illustrates another type of situation in which pneumoperitoneum is useful. The patient was a poor risk because of hypertension and poor nourishment. She had been explored for gastrointestinal bleeding with failure to find the bleeding site. The long right paramedian incision had broken down early following the operation and the patient was admitted to our hospital three months later with only thin ulcerated scars and skin covering a large defect in the abdominal wall. The problem presented was not that of a large hernia sac but rather a large defect from retraction of the edges of the wound, so that repair seemed likely to be difficult and inclined to a repetition of failure. Furthermore the patient had a history of myocardial infarction and heart failure and was considered to be a poor surgical risk from that standpoint. A month of pneumoperitoneum with protection of the thin scar by adhesive plaster succeeded in stretching the parieties so that repair was easy for the patient, and the edges could be overlapped without undue tension. During this period of preparation the adhesive plaster not only prevented a hernia from forming but allowed the skin wound to become completely healed and the scar to become quite thick and firm. There was no sign of cardiac decompensation or insufficiency during the period of preparation, during the hernia repair, or postoperatively.

DISCUSSION

Pneumoperitoneum in the preparation of patients with large hernias has made the term "inoperable" obsolete. Even before pneumoperitoneum the term "inoperable" was only a relative one, since many of these patients ultimately developed complications which forced an operation under the most unfavorable of circumstances. The mortality of hernia repair for patients with large hernias operated upon as emergencies has probably been as high as 50 per cent without the use of staged repair and pneumoperitoneum. The experience presented here is insufficient to indicate how much improvement can be expected in the mortality rate by a staged approach but it should be considerable. Since only the sac must be opened and closed and since release of the incarcerated contents plus occasional excision of damaged or devascularized bowel is the only surgery indicated during this initial emergency operation, the procedure can be relatively brief and nontraumatic. More important, postoperatively there is little if any increase in intraabdominal pressure. On the contrary, if the distention is gradual and by means of air, the patient can assist in determining the rate and intensity of the required stretching.

The proposal of Gross[4] regarding staged repair of omphalocele with preservation of the peritoneal covering of unreduced viscera has become accepted technique in the newborn infant. It is only necessary that surgeons use these same principles in their handling of emergencies associated with giant hernias. Once the emergency has been dealt with, a gradual stretching with pneumo-

peritoneum should be instituted in preparation for elective and controlled hernia repair which can even then be further staged if necessary.

When the surgeon finds insufficient room in the abdominal cavity because he has erred in not using pneumoperitoneum or has not used it long enough or intensively enough, he should accept a partial repair, in the case of incisional hernia, or resort to the technique of Ziffren and Womack[5] in the case of scrotal hernia. The latter procedure simply creates an incisional hernia for purposes of decompression until such time as room is re-established within the peritoneal cavity. Phrenic crush will give additional room but is ill advised since one of the serious complications of repairing large hernias without adequate preoperative re-establishment of abdominal domain is elevation of the diaphragm and respiratory embarrassment. Phrenemphraxis is not new but it is still recommended by some.[6] It is uncontrolled and temporarily, at least, irreversible in contrast to pneumoperitoneum, which is both controlled and reversible.

Less noxious is the use of patches of skin, fascia, or foreign material since these, of themselves, do not lead to increased intra-abdominal pressure with its deleterious side effects. With pneumoperitoneum available, and because it is so effective, these patch additions to the abdominal wall seem unnecessary and even undesirable. In most incisional hernias there is no real absence of abdominal wall. It has simply undergone a shrinkage of disuse. It should be the surgeon's objective to restore normal anatomical relationships and, when possible, to avoid leaving foreign materials in the wound.

On the other hand, if a hernia is repaired anatomically without abnormal tension and the repair appears insecure because of weakness of the tissues or the actual absence of part of the abdominal wall, then reinforcement or replacement is often mandatory.

There has been a tendency by some to use material such as dermis, wire screen, and so forth in every hernia repair. Most hernias do not require such adjuncts. Likewise, only occasional hernias are of the giant variety requiring pneumoperitoneum.

The experience presented by Koontz[2] as well as my own suggests that there is need to emphasize the importance of not compromising in the use of pneumoperitoneum once it has been instituted. If it is started it should be used for an adequate length of time and with sufficient intensity so that the desired increase in size of the abdominal cavity is attained before surgery is attempted.

Pneumoperitoneum is not a substitute for weight reduction when the latter is indicated. Pneumoperitoneum and weight reduction can be carried on simultaneously if a high protein diet is used containing the essential nutrients. The use of air in the abdominal cavity has a certain depressant effect on the appetite. The patient should be given a diet plan for weight reduction and the surgeon should insist that the patient comply. There is no harm in postponing operation and continuing pneumoperitoneum if the patient fails at first to cooperate. If the patient persists in eating excessively, he should be told that repair cannot be attempted as it might either fail immediately or lead to re-

currence ultimately. If the cooperation of the patient cannot be gained preoperatively, it is improbable that a maintained weight reduction can be expected postoperatively.

These patients should be informed beforehand that operative repair may need to be done in stages, just as patients are told that staged thoracoplasty is required or are advised of the necessity for more than one operation in the treatment of malignancies.

SUMMARY

An initial experience with pneumoperitoneum in the preparation of patients for repair of large hernias has been analyzed. Surgeons in this country should learn to use this simple and safe adjunct which has become an established and indispensable procedure in the minds of many South American surgeons. It can be carried out on an outpatient basis after the initial few days.

Emergencies that arise as complications of giant hernias can be treated with that minimum of surgery necessary for the emergency condition, and subsequent pneumoperitoneum can then be used as necessary for re-establishment of abdominal domain in preparation for a definitive and elective repair.

Pneumoperitoneum does not obviate the need for weight reduction or correction of other adverse influences that exist.

Pneumoperitoneum should be used with staged repair if inadequate room and/or abdominal wall is present for complete repair at the time of the initial operation.

In instances where the tissues are poor, reinforcement with fascia, tantalum mesh, or other appropriate material is not obviated by the prior use of pneumoperitoneum.

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OBSERVATIONS ON THE RELATIONSHIP OF OUTPUT TO INTAKE FOR TOTAL FLUIDS, NITROGEN, POTASSIUM, SODIUM, AND CHLORIDE FOR PERISURGERY PATIENTS UNDER PARENTERAL NUTRITION

J. H. Strickler, M.D., M.S.,* Carl O. Rice, M.D., Ph.D.,** and Alan E. Treloar, Ph.D.,*** Minneapolis, Minn.

(From the University of Minnesota Medical School)

VARIATION in clinical opinion with respect to desirable levels of intake of total fluids, nitrogen, potassium, sodium, and chloride for surgical patients is bounded only by the conservatism of the surgical profession. The literature on this subject is considerable, but, for the most part, it is fragmentary with respect to number of patients considered, if not also with respect to number of variables considered simultaneously.

From an assessment of balance observations collected on a large number of patients, we anticipate at least some measure of clarification of intake requirements and of the output behavior pattern of the nutritional elements currently under concern in parenteral feeding of surgical patients.

METHODS

A statement of concepts foundational to the present study, together with a preliminary discussion of certain of the data accumulated, has been given elsewhere.[21] That detail need not be repeated here, except to point out that 102 adult general surgical patients on complete parenteral feeding for an approximate average of five days each yield 488 patient days for determination in each of the items under study. Competent laboratory personnel, employing standard laboratory procedures under excellent conditions, give assurance with respect to reliability of the basic data. Nitrogen in urine and suction was determined by the method of Volhard, chlorides by the method of Schales and Schales, and the sodium and potassium determinations were made on the Beckman flame photometer.

Output comprised a total of urine, suction, bile, if any existed, and calculated insensible water loss. Stool output was not considered since on no oral intake such output was negligible. No patient with diarrhea was included in this study. Urine was collected by inlying catheter.

It is important to note that the needs of the patient from day to day were determined purely on the basis of clinical judgments, carefully arrived at after consideration of the condition of the patient at the time the orders were being written, with knowledge at hand of the intake of the patient during the preceding 24 hours, and also the patient's output in the same period.

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Studies conducted by Clinical Research Laboratory, St. Barnabas Hospital, Minneapolis, Minn.

*Clinical Assistant.

**Assistant Clinical Professor.

***Professor, Chairman of the Department of Biostatistics, School of Public Health, University of Minnesota.

PRESENTATION OF RESULTS

Since it is the purpose of this investigation to delineate the over-all picture and to define the findings for the 488 patient-days of observation, detailed tabulation of the individual determinations is deemed unnecessary. All objectives will be better served by presentation of the results in the form of scatter diagrams portraying the observed relationships. These are presented as Figs. 1 through 5, each of which will be discussed individually in the following paragraphs. We are not concerned herein with any attempts to measure intensity of association; the usual statistical measures of correlation have nothing but incidental interest in other processes and they will, therefore, not be mentioned further.

The scatters of points on the surfaces give the over-all picture, each dot representing the combined intake and output values for the variable of reference for a patient on one day of observation. The scales for measurement of both intake and output for each variable being the same, identical scales have been used for both intake and output axes in each diagram. As a consequence of this, a line at 45 degrees traversing each chart defines equal values of intake and output. This equivalence line is drawn lightly on each diagram.

The heavy straight line (of lower slope than the equivalence line) drawn continuously across each diagram is the "best fitting" straight line defining the relationship of output to intake *on the average,* over the range of intake values shown. This is a theoretical line arrived at mathematically, and usually known as the theoretical regression line. If it is acceptable as a graduation of the individual patient-day data as a whole, it should also agree within errors of sampling with the empirical regression line. The latter is also shown as a succession of circles joined segmentally by fine broken lines. Each circle defines the average output for a class range of intake, the small circle being placed at the mid-point of this range.

We shall now consider each variable in turn.

Fluid Balance.—It is obvious from inspection of Fig. 1, giving the relationship of fluid output to intake, that there is at least a modest degree of correlation between these two variables. Although far from perfect, this association is a long way from being negligible. For each liter increase in fluid intake, there is an average increase of nearly two-thirds of a liter in fluid output. Patients receiving the same amount of fluid vary in their output over a range of approximately 3 L. Any appearance of a tendency for this range in output to be less than 3 L. at the very lowest fluid intake levels may be deceptive and reflect rather the paucity of observations in that region.

It is interesting to note that, on the average, output equals intake at approximately the 2.75 L. level. Below this intake, patients tend to put out more than they assimilate. Dehydration would result. Above that point the reverse is true, on the average. The extremely high fluid intakes, it should be noted, belong to aberrant conditions, consideration of which appropriately

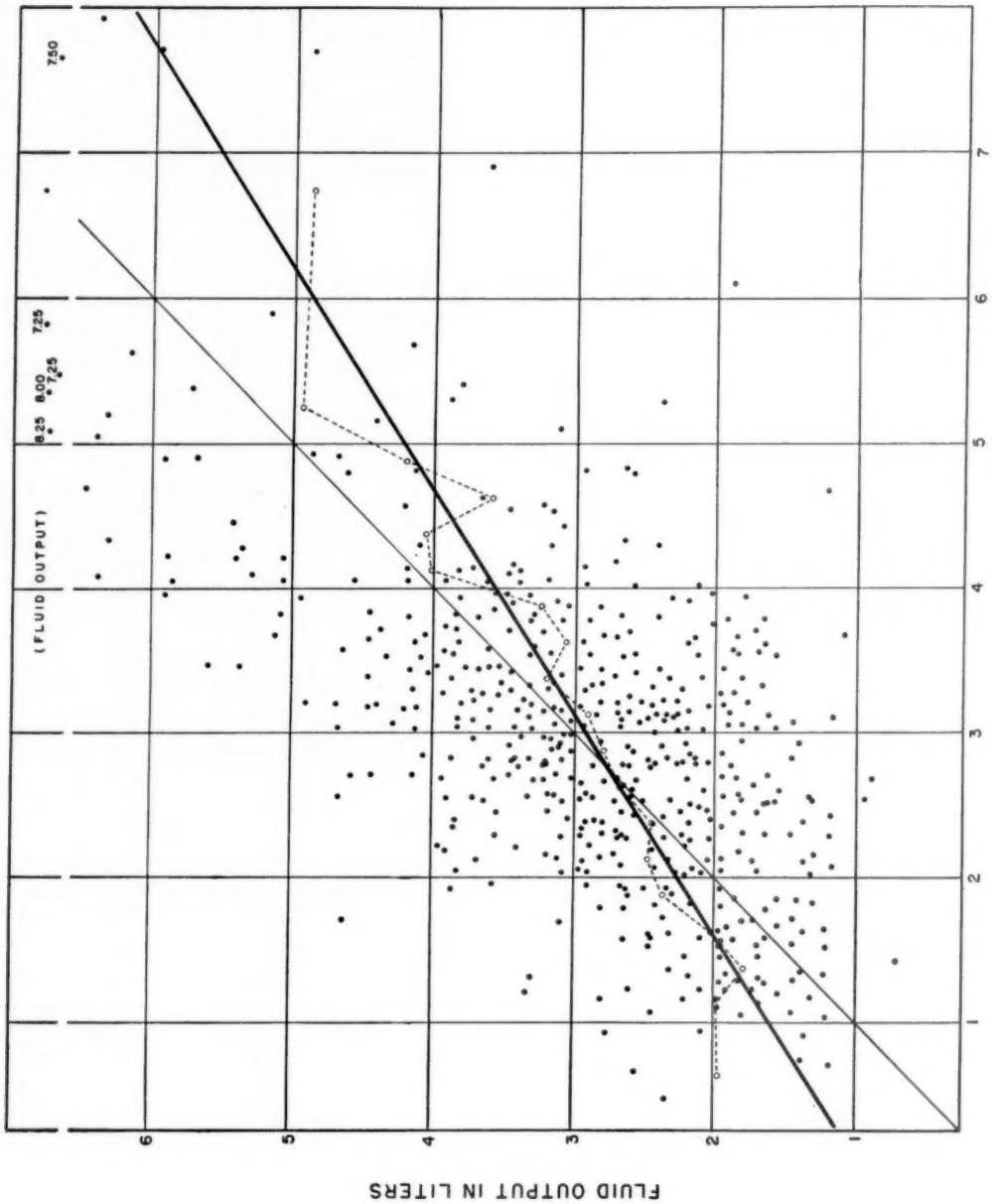
750
725
800
825
(FLUID OUTPUT)
FLUID OUTPUT IN LITERS
FLUID INTAKE IN LITERS

Fig. 1.

should be suppressed in favor of concentration of attention on the more usual levels. This fluid requirement corresponds to that which has been designated by others as the optimum daily fluid requirement.

Nitrogen Balance.—Fig. 2 presents the relationship of output to intake for nitrogen, in some measure reflecting physiologic activity of the patient with respect to synthesis and destruction of protein. It will be noted at once that

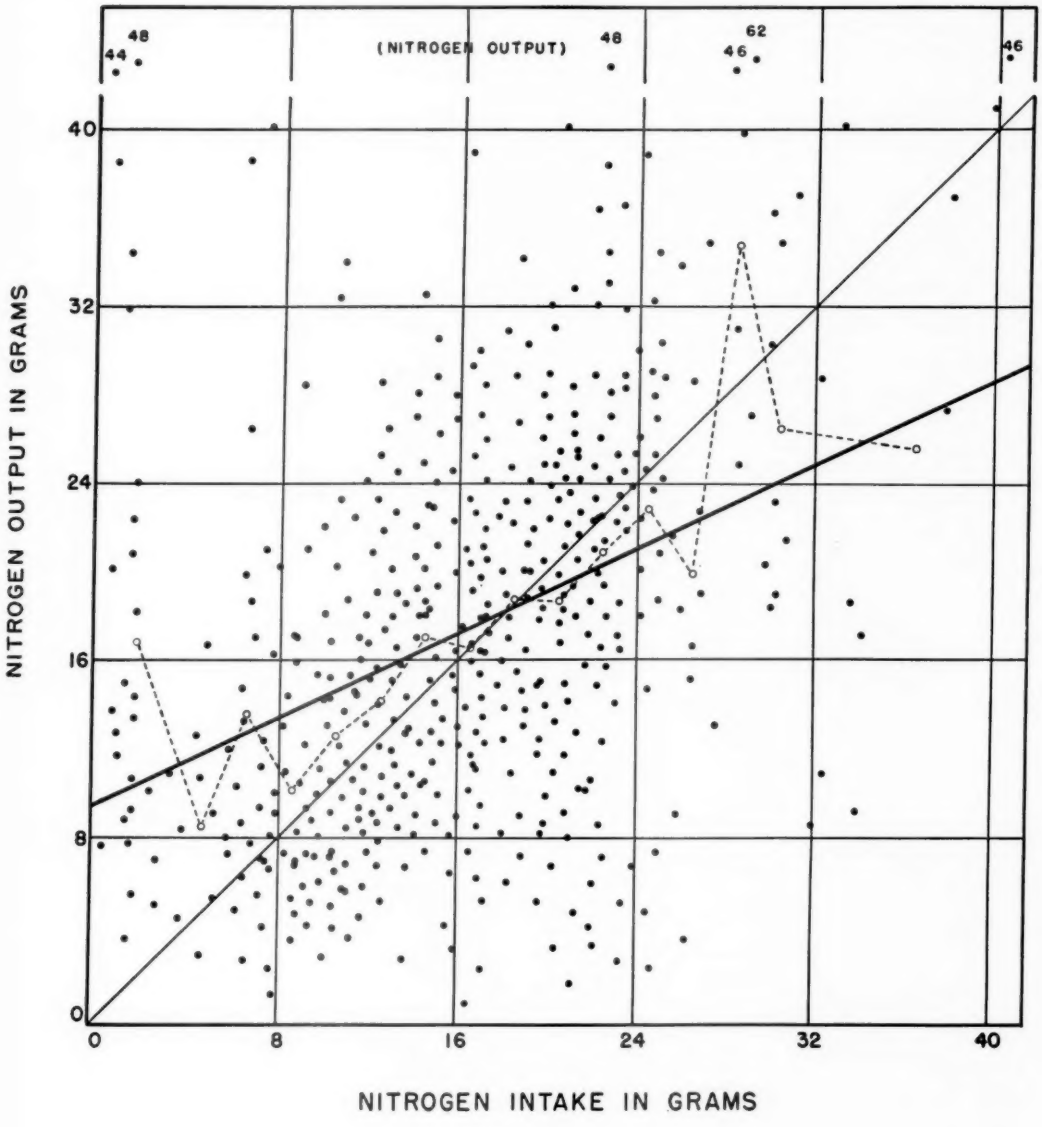

Fig. 2.

the association between intake and output of nitrogen, with respect to the metabolism of protein, is of a much lower order than in the case of the fluid balance. At first glance it might seem that there is no association at all, but this is a false impression. The theoretical regression line, which is in sub-

stantial agreement with the succession of the empirical class averages, has at least a modest slope. On the average, nitrogen output equals intake at a daily assimilation of approximately 18 Gm. On the average, also, an increase of 1 Gm. in nitrogen intake is accompanied by an increase of slightly less than 0.5 Gm. in nitrogen output.

The range of individual outputs for any given level of intake with respect to nitrogen is astonishingly wide. Indeed, only one output in the series exceeds those of patients who were on essentially zero intake. It is too easy,

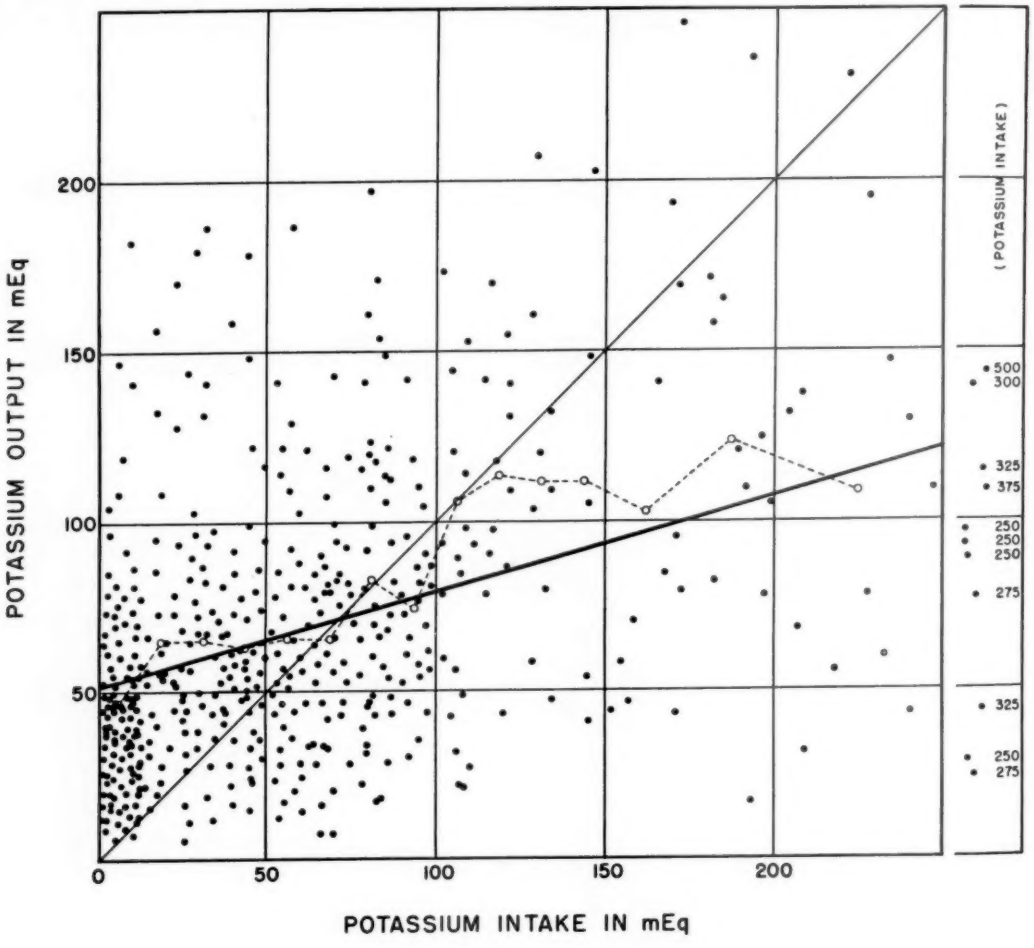

Fig. 3.

however, to emphasize the extreme deviate in a study of this character, and this should be guarded against. Indeed, there is an atypical character to the minimal nitrogen intake group in our data, and this is due primarily to two patients only. It is important to note that, were it not for the wide scattering of cases with zero nitrogen intake having substantial outputs, the slope of our theoretical line of average dependence would be somewhat higher than it is. Our judgment is that the theoretical graduating line is essentially straight through the middle of its course, flattening perhaps at each end enough to introduce a slight sigmoid curvature to this regression. Continuing

studies should disclose whether or not this is so. If, eventually, we become able to construct such a sigmoid curve for the nitrogen relationship, we should find it in reasonable agreement with our present straight line through the range from 12 to 24 Gm. intake.

Potassium Balance.—The relationship between output and intake for potassium is portrayed in Fig. 3. Perhaps the outstanding characteristic here is the persistence of the body in putting out potassium over a modest range,

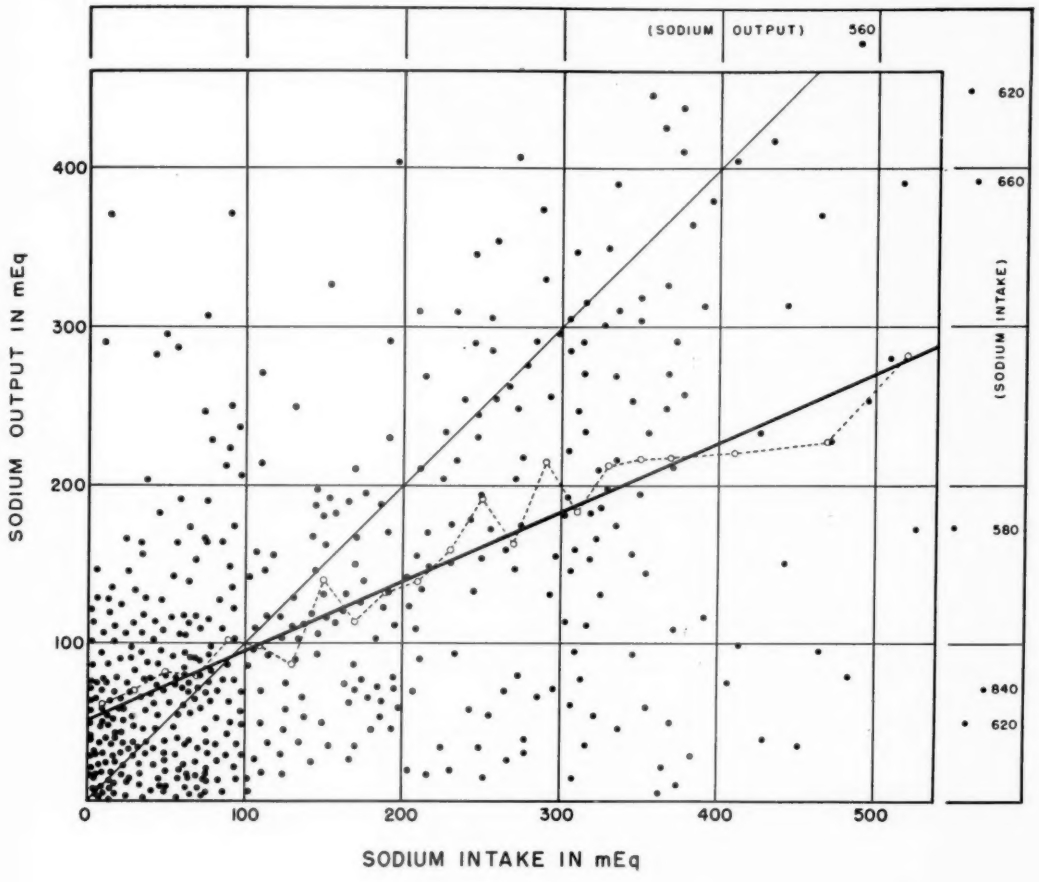

Fig. 4.

on the average, regardless of the intake. Approximately one-fourth of our intakes were essentially at zero level, yet outputs averaged almost 50 meq. and were distributed over a range up to 180 meq. for the day. The empirical average quickly reaches and remains at approximately 70 meq. output per day until intake assumes that level. Output then seems to rise almost abreast of input, on the average, until a new level of approximately 120 meq. per day output is reached. This output seems to be maintained, on the average, in our data for all higher intakes, but sparsity of data forbids any assumption that this will continue to be observed as the series of data increases.

The implication here seems to be clear. Lacking any evidence that the potassium level of a patient needs to be changed, an initial intake of 50 meq.

per day is indicated. Intakes much above twice this amount may perhaps be expected, on the average, to be largely retained by the body.

These findings may appear to conflict with accepted standards for the Potassium-Nitrogen ratio, but it is to be remembered that this is a group of ill patients observed immediately before and after surgery.

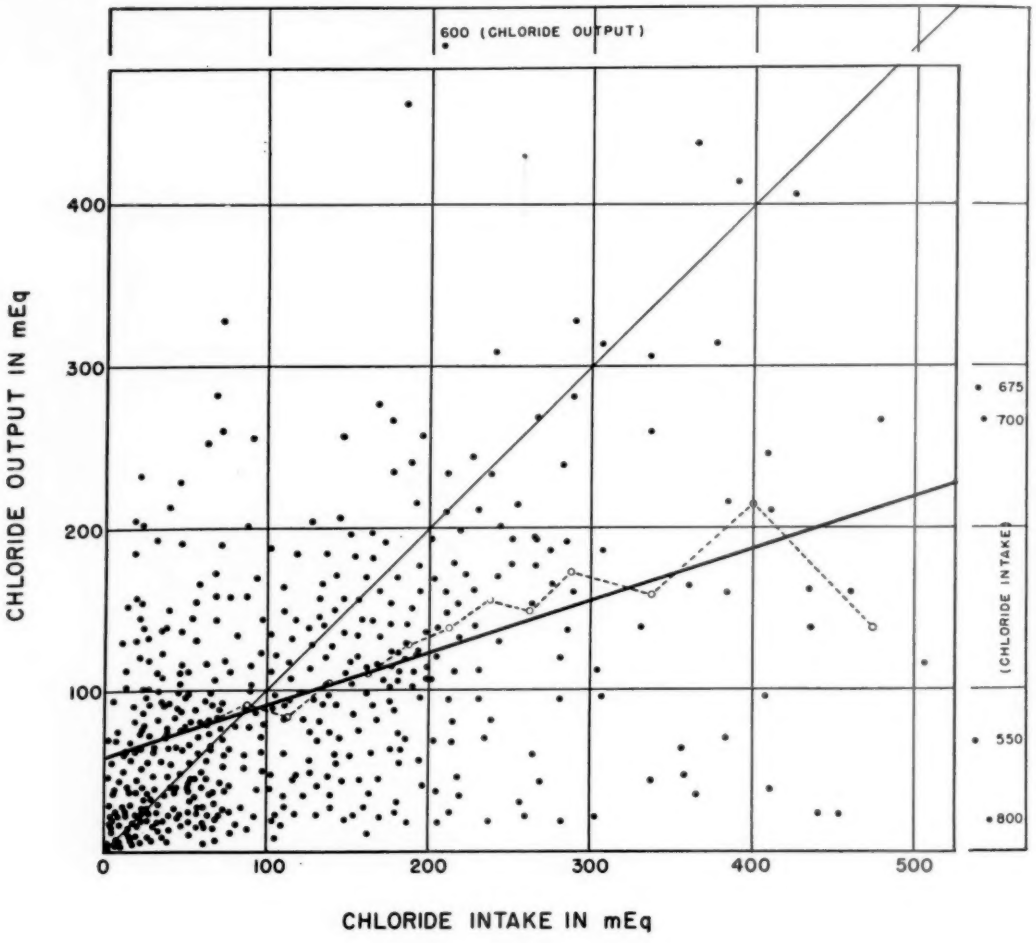

Fig. 5.

A straight theoretical graduation line falls short of being satisfactory for this variable except at the low intake levels. As the potassium intake progressively approaches 100 meq. per day, there may be a slightly increasing tendency for potassium to be discharged from the system (Fig. 3). Around 100 meq. intake per day there seems to be a sharp rise in output, followed perhaps by a reasonably constant potassium output, on the average. Thus again we face the possibility of a sigmoid curvature in the regression line. More definite in its suggestive character than in the case of nitrogen, it is certainly a provocative finding which we shall explore further in subsequent analysis, especially in relation to sodium and chloride.

Sodium Balance.—The relationship of output to intake with respect to the sodium ion is certainly simpler and more easily comprehended than in the case

of the potassium ion. The results for sodium are given in Fig. 4, where it is clear that a straight graduating line is reasonably satisfactory for the average relationship of output to intake until the highest levels of sodium intake are reached. Output balances intake, on the average, at slightly under 100 meq. per day. As with potassium, and, indeed, with fluid and nitrogen as well, the body tends, on the average, to put out more than it takes in when the intake is at a low level. This picture is reversed when intake reaches high levels. Although somewhat general, this statement expresses a statistically expected consequence of intermediate correlation.

Tremendous individual variation is again a conspicuous feature with respect to balance in this ion. Some patients on extremely high sodium intake retain practically all of it throughout the day on which it is administered. Conversely, some patients receiving very little sodium expel strikingly large amounts, but the average relationship is rather markedly straight, in contrast to that for potassium. A unit increase in intake of sodium is accompanied by a nearly one-half unit increase in output, on the average, for this ion. It will be noted that input of sodium is balanced by output at approximately 90 meq. on the average.

In a later paper we expect to give detailed attention to the interrelationship between sodium balance and potassium balance.

Chloride Balance.—Geometrically speaking, there is a closer basis of comparison between the intake-output relationship for chloride, portrayed in Fig. 5, and that for sodium, given in Fig. 4, than for any other pair of relationships discussed herein. It will be noted that, on the average, chloride output matches intake a little less than in the case of sodium, but otherwise the two scatters are highly comparable. Chloride output is equal to intake, on the average, at the level of approximately 90 meq. per day. There is a somewhat greater tendency for patients to retain chloride, regardless of intake, in the sense that, whereas the intake of chloride ranged roughly over the same scale values as the intake of sodium, the output of chloride exceeded 300 meq. per day more rarely than did the output of sodium. When the highest chloride intake cases are ignored, the average relationship is graduated very satisfactorily by a straight line. We would suggest that the straight line is adequate up to a level of approximately 400 meq. intake of chloride per day, a unit intake being accompanied by a one-third unit output, on the average.

DISCUSSION

We observe from these data (Figs. 1 to 5) that the average surgical patient requires 2.75 L. of fluid, 18 Gm. of nitrogen, 70 meq. of potassium, 90 meq. of sodium, and 90 meq. of chloride in each twenty-four hour period in order to balance the output, that is, to be in a state of equilibrium. This is indication that a polyionic solution containing these quantities of electrolytes in 2.75 liters of fluid should provide the average daily fluid and electrolyte requirements. This is, however, only a statement of over-all average.

It is very important to consider the individual as such, and especially the aberrant situations which may arise. Many specific cases vary greatly from the average situation. Thus, a mere glance at the charts will reveal that any specific patient may deviate widely from the usual and therefore the problem of the ideal handling of any particular clinical problem would in our opinion necessitate a knowledge of specific output determinations.

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MECHANISMS OF SODIUM REGULATION IN THE SURGICAL PATIENT

BERNARD ZIMMERMANN, M.D.,* JAMES H. CASEY, M.D.,** AND
HENRY S. BLOCH, M.D., MINNEAPOLIS, MINN.
(From the Department of Surgery, University of Minnesota)

BACKGROUND

THE Metabolism of Sodium Ion Following Surgery.—That patients who have undergone surgical procedures tend to restrict the excretion of sodium in the urine has been known for many years. This was pointed out by Trout[49] in 1913 in connection with proctoclysis, and the hazards of giving large amounts of sodium chloride were emphasized by Dr. Matas[32] who was largely responsible for the introduction of continuous intravenous fluid therapy in this country. The report of Jones and Eaton[26] in 1933 under the title of "Postoperative Nutritional Edema" described a clinical situation which was common during the period when "physiological" saline solution was widely used by surgeons as a hydrating fluid. It was not until 1945, when the balance studies of Coller and his associates[9, 10] demonstrated the powerful tendency for retention of sodium associated with high levels of potassium excretion, that surgeons began to take seriously the possible hazards of administering too much sodium ion to patients following surgery. By this time many studies of nonspecific response to trauma had been in progress. The experimental work of Selye[42, 43] in animals and the extensive metabolic study of Cuthbertson,[11] Albright,[1] and Howard[21] and others had clearly demonstrated that among the numerous effects of trauma of a degree comparable to that of major surgery, was a tendency to the retention of sodium ion coupled with an excessive excretion of potassium. That this and several other aspects of the altered metabolism of the postoperative patient was the result of a form of physiologic hyperadrenalism was logically suspected and was confirmed by the finding of increased amounts of hormones of adrenal origin in the urine of postoperative patients.[51, 52, 53] The development of the eosinophil count as an index of the activity of the adrenal cortex served also to confirm this concept and to some extent to delineate the duration and the adequacy of postoperative adrenal response.[27, 42]

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*American Scholar in Cancer Research, American Cancer Society.

**National Cancer Institute Trainee.

Despite these findings, proving without question that adrenal hyperactivity does exist in the postoperative state, little had been learned concerning the mobilization of specific endocrine factors which might be concerned exclusively with electrolyte balance. These metabolic derangements do not all occur simultaneously and adrenal hormones do not all have the same type of activity. Further studies relating endocrine phenomena to alterations in electrolyte balance clearly would have to deal with specific hormones and with the mechanisms underlying their mobilization. A real understanding of such factors would require the measurement of something much more closely related to electrolyte balance than, for example, the eosinophil count. This is a much more complex problem than merely demonstrating that adrenal hyperactivity does occur. Nevertheless, if we are eventually to deal with the mechanisms of electrolyte regulation or to take them into consideration in anticipating the needs of patients, a specific approach to the regulatory machinery must be attempted. Experiments which follow represent some ventures in this direction. Only a few investigations have been directed toward an attempt to correlate known indices of adrenal function with electrolyte balance. Hardy[17-19] attached considerable significance to the fact that the duration of oliguria in the postoperative patient ran closely parallel to the postoperative eosinopenia and he found a similar relationship between the eosinophil level and the fluid loss from gastrointestinal secretion. Johnson and co-workers[25] (see below) found evidence suggesting the presence of hormones with electrolyte activity resembling desoxycorticosterone. Moore[36] pointed out that positive sodium balance persists for several days after nitrogen balance and glycocorticoid excretion have returned to normal and suggested that sodium is under the control of a separate endocrine mechanism.

The Fate of Extracellular Sodium.—Consideration of sodium balance cannot be made without reference to changes that occur inside the body in association with alterations in external balance. It has long been recognized that following surgery, severe forms of stress, and infection, patients tend to have low extracellular levels of sodium and chloride. That sodium disappears from the plasma, as well as the urine, is in a sense paradoxical and has, in fact, been referred to by Moore[37] as a "sodium paradox." Fig. 1 illustrates the extent of some of these changes. It represents the average data on extracellular electrolyte levels following 40 uncomplicated surgical cases. Preliminary data on fewer cases were reported at the Surgical Forum in 1952.[58] It is observed that the sodium value drops immediately and is lowest on the first or second postoperative day. Chloride concentration also drops and does not rise quite as rapidly as does the sodium. Potassium concentration is depressed throughout the entire postoperative course. The latter is to some extent outlined by the course of the eosinophils which follow a rather consistent pattern returning to normal within the fifth or sixth day after surgery. Fig. 2 is a similar study of 16 patients who had very extensive and prolonged cancer surgery,

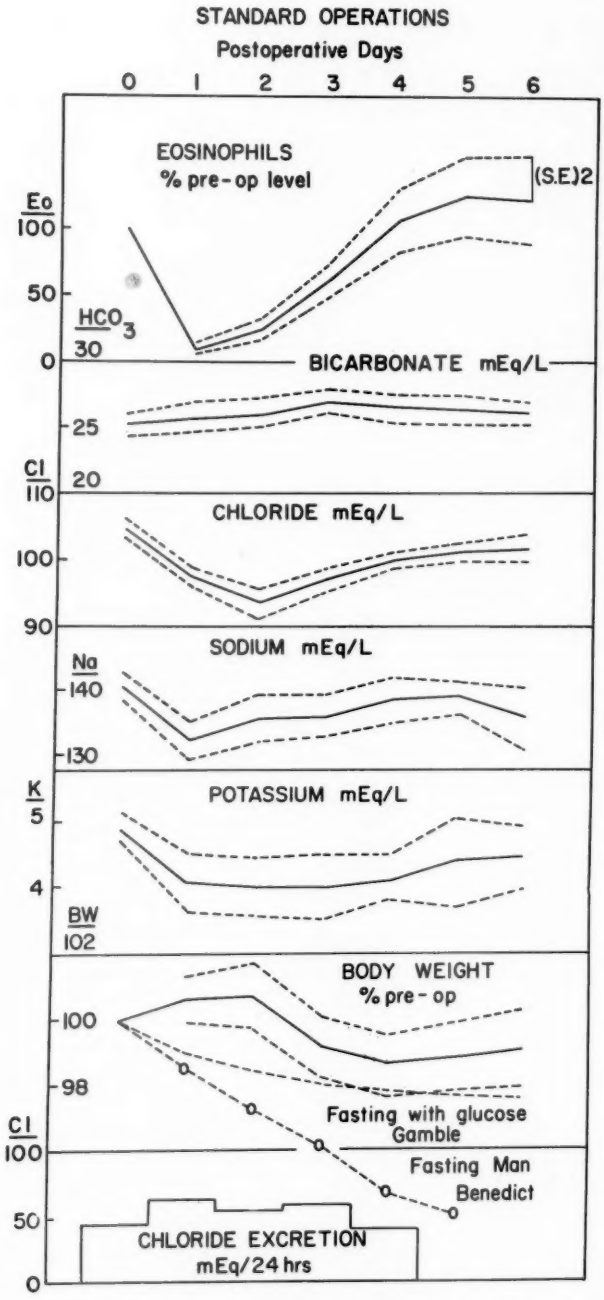


Fig. 1.—Mean values for plasma electrolytes, eosinophils and body weight following 40 uncomplicated major operations illustrating tendency for reduction in sodium and chloride concentrations and maintenance of body weight above that which would be expected in non-operated subjects with similarly restricted caloric intakes.

$$\text{wt.} = \frac{\text{wt. at time t (100)}}{\text{Pre-opr. wt.} - \text{spec. wt.}}$$

none of whom suffered serious postoperative complications. This study is of interest because it demonstrates that the usual depression of sodium and chloride values is exaggerated following the extensive operations, whereas the postoperative course, as outlined by the eosinophil depression, is very little changed. The relationship of this pattern of sodium reduction to the incidence and timing of postoperative "water intoxication" has been discussed elsewhere.[64]

The meaning of findings such as these is only partly understood and still requires investigation. Part of the explanation may be that a retention of water has caused a dilution of extracellular electrolytes. That this is true is suggested by the last line on Figs. 1 and 2 which shows the course of the body weight following these operations. This weight change is plotted in Fig. 1 concurrently with the weight course one might expect in individuals who did not have operations, but were maintained on the amounts of water and glucose which postoperative patients normally receive. Such a weight experiment has not actually been done but was calculated from the data of Gamble[15] in which water balance was related to various degrees of fasting. It is apparent that, in relationship to such a base line, the human being following surgery exhibits abnormally positive water balance. Furthermore, tolerance to excess water loads is severely decreased.[38, 64] This is important for a number of reasons, one of which is its relationship to the extracellular sodium level. It is generally agreed, however, that such an explanation does not adequately clarify the apparent disappearance of sodium. The only other explanation is that the sodium must leave its normally-extracellular position. To do this it must either go into the cells of the body, or must be translocated to a reservoir or depot which has not yet been discovered. In an attempt to elucidate these possibilities Dr. Herman Delancy,[62] working in this laboratory in 1953, did some interesting studies. He measured the extracellular space preoperatively and on the first and second postoperative days by the concomitant use of two substances: sodium thiocyanate and sodium thiosulfate. He picked these because sodium thiocyanate behaves in a manner very similar to chloride and could be expected to follow this ion if the physiologic circumstances were to force the chloride ion to take up abnormal locations. Sodium thiosulfate, on the other hand, does not bear this biochemical relationship to chloride and its distribution is believed to be more closely related to the "anatomic" extracellular space. By neither of these techniques was he able to demonstrate an increase in the extracellular space which accounted satisfactorily for the apparent dilution of sodium and chloride. When extracellular sodium and chloride were measured using the thiosulfate space, an average deficit of 187 meq. of sodium and 132 meq. of chloride developed during the first twenty-four hours after surgery. He was compelled to the conclusion that, during this short period of time, sodium ion must have moved into the cell. But what of the chloride? If this had been the case for chloride the normal difference between

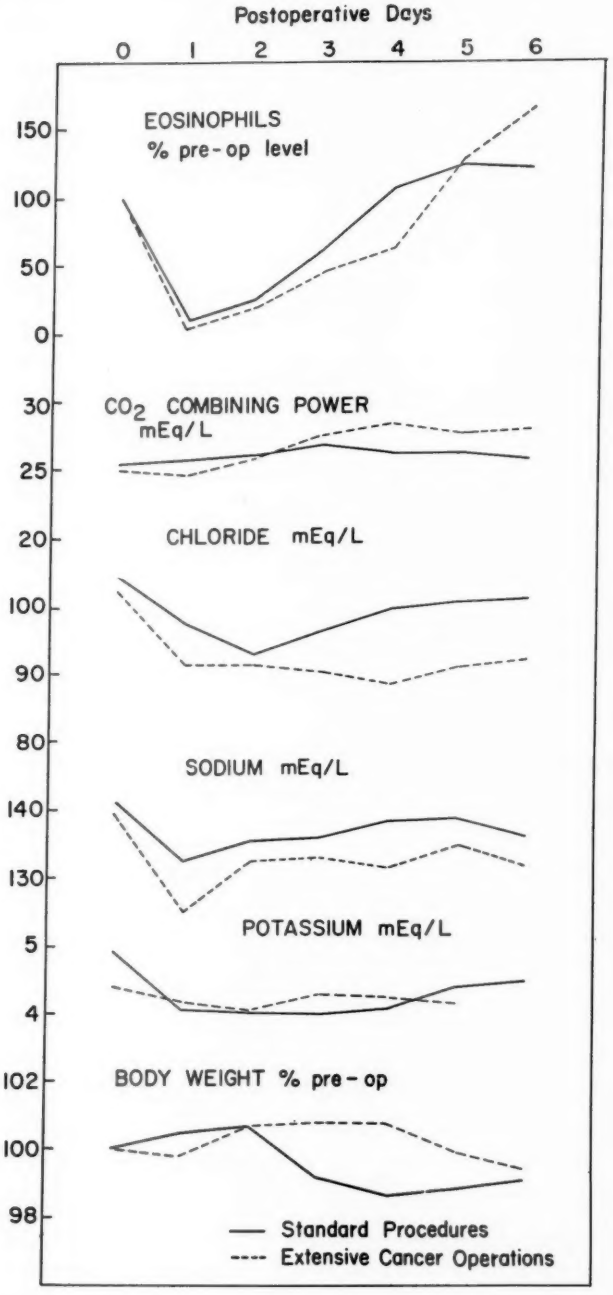


Fig. 2.—Mean values for electrolytes, eosinophils, and body weight in 16 uncomplicated, very extensive operations for visceral malignancy. Dotted line indicates standard operations (Fig. 1) for comparison.

the thiocyanate space and the thiosulfate space (the latter is usually about 2 L. greater) would have increased if chloride had been translocated to an intracellular position. This did not occur. We were left, therefore, with no satisfactory scheme to explain the rapidly changing picture which characterizes the first and second postoperative days. In connection with intracellular shifts of sodium it is probably important to distinguish the problem concerned here from that of the increasing intracellular sodium which is associated with chronic potassium deficiency. During the first two postoperative days, when the sodium level is lowest, great losses of potassium have not occurred. An alkalosis such as is associated with potassium deficiency, though not uncommon after surgery (Fig. 1), does not present itself until several days later. The possibility has been entertained that discrepancies of this sort may be explainable by changes in some large sodium-containing reservoir such as the skeleton, the crystal lattice of which holds as much as 30 per cent of the total body sodium.[35] Our recent studies of bone sodium following surgery suggest that changes in this reservoir, though important in prolonged depletion states, are not of sufficient magnitude nor speed to account for the rapid changes associated with operations.[5] We must be content for the moment with the concept that serum sodium drops probably for several reasons which have to date been inadequately evaluated and proceed to the question of why sodium is withheld from the urine. We have dwelt on this first phenomenon because it may have a bearing on the regulation of some of the hormonal mechanisms which remained to be discussed.

The Regulation of Hormones Concerned With Sodium and Potassium Balance.—It is clearly established that those hormones of the adrenal cortex which are primarily concerned with organic metabolism are under the control of the anterior hypophysis. The release of ACTH from the pituitary gland stimulates the secretion from the adrenal gland of glycocorticoids and particularly 17-hydroxycorticosterone or compound F. The corticotrophic mechanism of the pituitary in turn is controlled by certain centers in the hypothalamus and eventually by neural and perhaps also hormonal stimuli connecting the central corticotrophic mechanism with the peripheral portions of the body which are subjected to stress.[22, 29] There is a considerable amount of evidence, however, that the regulation of sodium and potassium balance is not under the control of the pituitary. Earlier evidence for this was based on work in rats, in which animals the zona glomerulosa appears to be primarily concerned with electrolyte regulation. Changes in the size of this portion of the adrenal can be readily induced by alterations in the sodium-potassium ratio of the diet, but such changes are not caused by either ACTH administration or hypophysectomy.[13] In this species, therefore, it appears that the mineral-regulating portion of the adrenal approximates a separate organ responsive only to alterations in the blood electrolytes themselves. In the process of attempting to elucidate the hormonal machinery for sodium regulation in surgical patients,

it seemed important to know what relationship electrolyte regulation in the human bore to the anterior pituitary. An experiment was devised which was reported at the Surgical Forum in 1952.[63] Part of the results are shown in Fig. 3. This experiment involved human subjects placed on diets deficient in sodium (9 to 13 meq. per day) but with very high potassium content (250 to 300 meq. per day). Such an abnormal sodium-to-potassium ratio of the diet could be expected to impose a severe burden on the adrenal electrolyte-regulating mechanism. Indeed a patient with adrenal insufficiency would rapidly

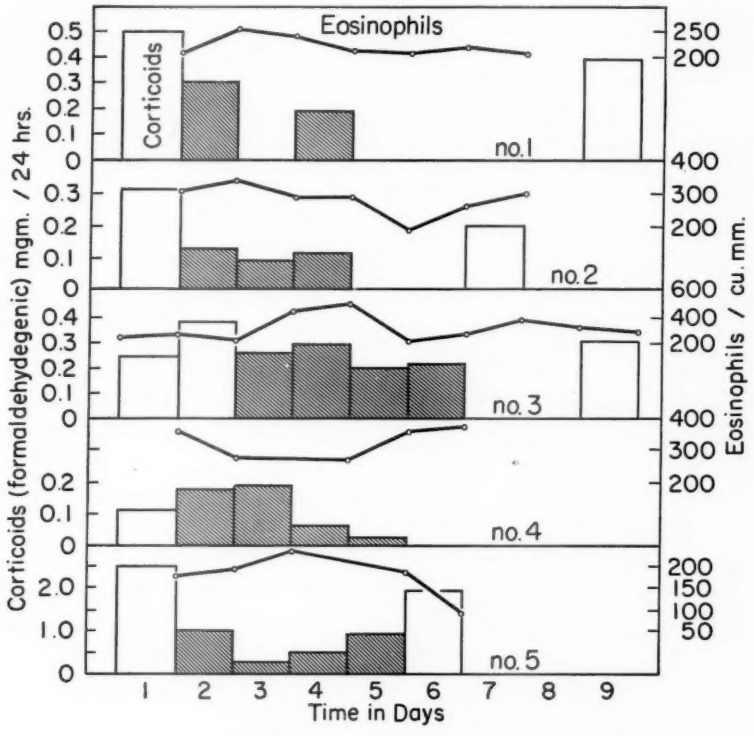
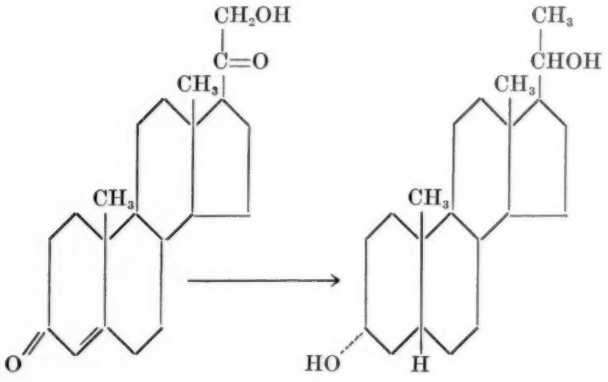


Fig. 3.—Effect of low sodium, high potassium intake on blood eosinophils and urinary formaldehydegenic corticoids.

succumb to such a regimen. Blood eosinophil levels and urinary formaldehydegenic corticoid determinations were made because these are both exquisitely sensitive indices of pituitary stimulation through ACTH. It turned out that eosinophil levels were not depressed under the circumstances of this treatment and urinary formaldehydegenic corticoids were decreased rather than increased under the experimental circumstances. The conclusion seems warranted that the human adrenal does not require the participation of ACTH to enable it to respond to the necessity for sodium conservation. In that regard the situation was similar to that described above for the rat. Although the nature of the compounds involved in this regulation were unknown, at least one property of them could be stated. They appeared to be produced

independently of ACTH. The finding was perhaps not surprising because it is well recognized that patients with panhypopituitarism are not subject to the same electrolyte difficulties as individuals with Addison's disease. Our experiments, of course, do not exclude the possibility that mineral-regulating corticoids are under the control of a second corticotrophic hormone—a role which some think is played by growth hormone.[41]

Desoxycorticosterone.—Until recently the most potent pure sodium-retaining substance was desoxycorticosterone. This compound, originally obtained synthetically, has been found in small amounts in beef adrenals and in adrenal vein blood.[39] The matter of its significance as a true adrenal hormone has always been questioned. Because of its potency, desoxycorticosterone was frequently suggested as the substance underlying the sodium retention which characterized the response to surgery. Johnson and co-workers[25] in 1950 strongly suggested that this was the case on the basis of findings of alterations in the sodium-potassium ratio in sweat of postoperative patients which were characteristic of both ACTH administration and desoxycorticosterone. This evidence is, of course, very indirect and the effects observed could have been caused by any substance possessing such activity. Unfortunately, little is known about the metabolic end-products of desoxycorticosterone and its relatives. It has been observed, however, in both animals and human beings, that administration of desoxycorticosterone results in an increased urinary excretion of pregnanediol glucuronide and some hypothetical mechanisms for the conversion:



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(I) 11-desoxycorticosterone and (II) pregnanediol have been suggested.[12, 20, 57] Studies of metabolism of this substance in women who had undergone ovariectomy and adrenalectomy for advanced mammary carcinoma made it possible to confirm the urinary pregnanediol response to desoxycorticosterone in human subjects (Fig. 4), and it seemed to be worth while to look into this substance in the urine of postoperative patients. Studies were done on seven patients who underwent elective surgical procedures. Only male patients were considered because of the well-known cyclic production of pregnanediol related to pro-

gesterone secretion in the female. Fig. 5 illustrates the results of this experiment. It is quite apparent that pregnanediol excretion did increase immediately following surgery, followed a pattern not unlike that of formaldehydegenic corticoids, and was closely related to the postoperative course as outlined by the depression of the eosinophils. Clearly from this experiment one could conclude that desoxycorticosterone may be mobilized in the postoperative patient. One could not, of course, assume that desoxycorticosterone is the only precursor for which the urinary pregnanediol was a metabolite. We could rule out two precursors because numerous studies on both intact and adrenalectomized subjects indicated that the administration of cortisone and hydrocortisone (compound F) never caused this elevation of urinary pregnanediol. ACTH administration, on the other hand, did result in pregnanediol output over periods of time roughly

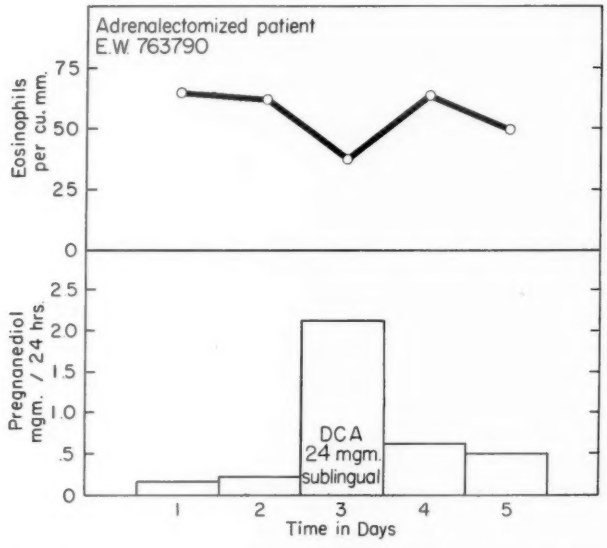


Fig. 4.—Response of urinary pregnanediol to desoxycorticosterone administration in adrenalectomized, ovariectomized patient.

corresponding to the concomitant excretion of formaldehydegenic corticoids and the depression of blood eosinophils.[59] This finding came as somewhat of a surprise in that we were looking for a substance which was not susceptible to regulation by the adrenal corticotrophic hormone. On the basis of these experiments, therefore, we had to admit the possibility of desoxycorticosterone but could not clearly prove its presence. We could come to one definite conclusion, however, and that is of some interest. Some substance other than cortisone and hydrocortisone was produced by the adrenal under stimulation of both surgery and ACTH. The nature of this substance or substances remains unknown. A further bit of evidence regarding the desoxycorticosterone hypothesis appeared subsequently in connection with the aldosterone experiments described below.

Aldosterone and Other Substances Chromatographically Demonstrated.—Prior to 1953 a growing body of evidence indicated that there existed in human

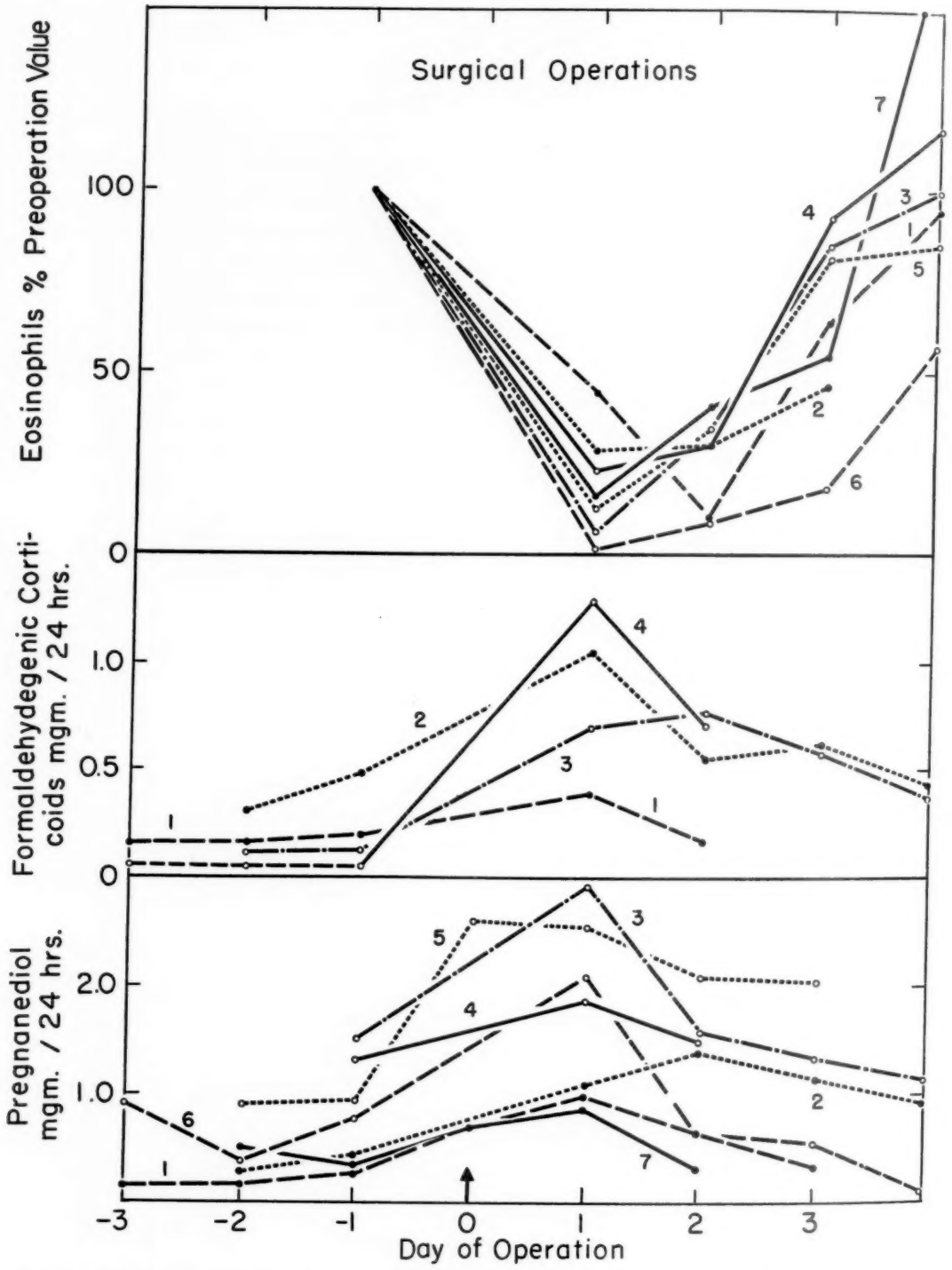
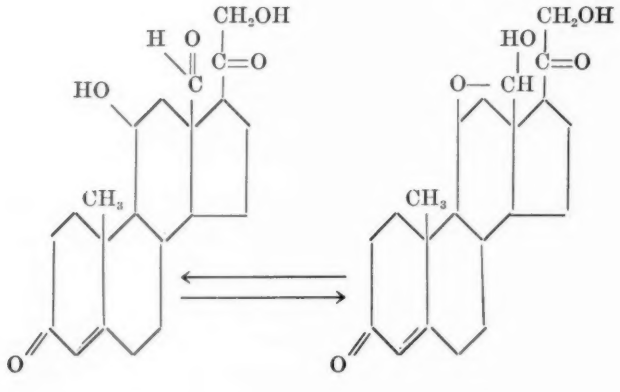


Fig. 5.—Excretion of pregnanediol and formaldehydegenic corticoids and the blood eosinophils following major operations.

urine a sodium-retaining factor which was much more powerful than any of the known crystalline adrenal corticoids including desoxycorticosterone. This material, which can be assayed only in the adrenalectomized rat, was extensively studied by Luetscher,[30] Gordon,[7] and others[6, 34] and was found to be greatly increased in the urine of individuals suffering from various states characterized by sodium retention such as nephrosis, hepatic cirrhosis, congestive heart failure, and toxemia of pregnancy. An important chemical distinction between this salt-retaining factor and desoxycorticosterone was made by partition between water and benzene. The salt-retaining factor entered the aqueous phase while desoxycorticosterone was found in the benzene solution.[4] In the meantime, it had not been forgotten that adrenal cortical extract after all known crystalline steroids had been removed still retained a powerful life-maintaining material in the "amorphous fraction." Studying adrenal extracts by means of paper chromatography and rat bio-assays, Tait, Simpson and Grundy[47] concluded "the mineral activity in adrenal extract is due to a highly active compound or compounds which is not one or a combination of the known crystalline corticosteroids." This discovery was followed by the demonstration of a sodium-retaining principle in adrenal vein blood.[44] The isolation and crystallization of the hormone which became known as electrocortin was a result of the combined efforts of the British investigators Simpson and Tait in collaboration with Wettstein and Neher of the Ciba Laboratories and von Euw and Reichstein[45] of the University of Basel. As a result of this work 22 mg. of a new crystalline hormone were isolated from 500 kg. of beef adrenals. Almost simultaneously the same compound was isolated in the amorphous form at the Mayo Clinic by Mattox, Mason and Albert.[33] Since investigation of the structure of electrocortin demonstrated it to be closely related to corticosterone differing from the latter only by an aldehyde instead of a methyl group on carbon–atom–13, the compound was renamed aldosterone.[46] It exists in at least two forms: the free aldehyde (I), and the cyclic hemiacetal (II).



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Biologic studies of this material demonstrated it to be 25 to 30 times as active in sodium retention as desoxycorticosterone and about 5 times as active in regard to potassium excretion.[14, 16] It has relatively little effect on carbohydrate metabolism.

Semispecific methods are now available for the quantitative assay of aldosterone. The best ones utilize preliminary chromatographic separation of the steroids in urinary extracts, the final quantitation being carried out on the basis of the urinary electrolytes of adrenalectomized rats into which the test materials have been injected. In the brief time that such methods have been available some very interesting facts have emerged regarding the physiologic regulation of this hormone. In addition to being present in increased amounts in the previously mentioned conditions, it has been shown largely by the work of Luetscher and his colleagues[2] that it is usually present in small amounts in the urine of normal individuals as well as individuals with hypopituitarism but is absent in Addison's disease. The output is not significantly stimulated by ACTH although it has been reported by Venning[54] that an increase in urinary aldosterone follows administration of growth hormone. Of particular interest is the fact that subjection of individuals to a low sodium diet does result in a strikingly increased output of aldosterone.[31] The importance of investigating this material in the urine of postoperative surgical patients is apparent.

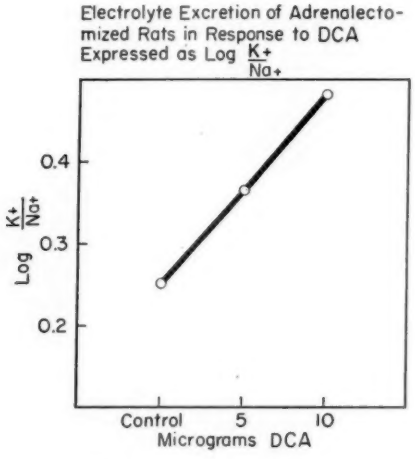

Fig. 6.—Relationship of log $\frac{K}{Na}$ to standardization doses of desoxycorticosterone in urine collected from adrenalectomized rats for five hours after desoxycorticosterone injection. Most nearly linear and hence most useful portion of curve is shown here, i.e., range of log $\frac{K}{Na}$ values corresponding to from 0 to 10 μg desoxycorticosterone.

Aldosterone experiments: Twenty-four-hour urines of patients before and after operation were hydrolyzed with beta glucuronidase and continuously extracted with chloroform.[8] The chloroform was removed and the residue redissolved in alcohol and run through the benzene-water partition of Talbot.[48] The material which remained in the aqueous phase was extracted with chloroform and subjected to paper chromatography in the propylene glycol-toluene system of Zaffaroni.[3] Portions of the strip were treated to produce color re-

actions with antimony trichloride. From the untreated portions a section of the paper including materials slightly more polar than compound E was eluted with alcohol and assayed on rats which had undergone adrenalectomy four days previously and subsequently been maintained on saline drinking water. Aliquots of extract corresponding to 20-minute urine volumes of the patient were injected into rats and the urine collected for five hours after injection. Groups of 10 rats were used for each urine sample as well as for the controls and desoxycorticosterone standards. The value log $\frac{K}{Na}$ for the 5-hour rat urine was found to be the most critical quantity for measuring aldosterone and gave most nearly linear relationships to standardization doses of desoxycorticosterone. Fig. 6 is an example of such a standardization curve for values of log $\frac{K}{Na}$ usually encountered in these experiments. This method of assay and calculation on the basis of log $\frac{K}{Na}$ was similar to that described by Johnson.[24] The details of the technique are in press.[61]

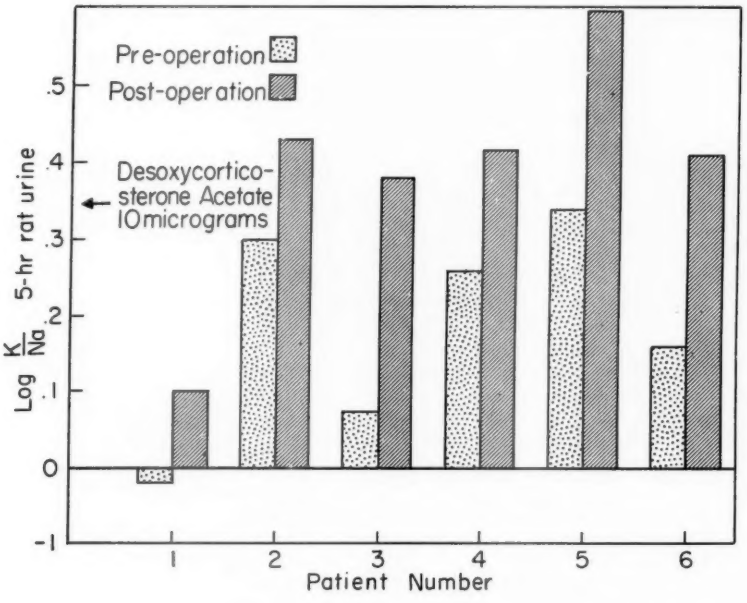

Fig. 7.—Excretion of aldosterone before and after operation as indicated by values of log $\frac{K}{Na}$ for the 5 hour urines of adrenalectomized assay rats.

Fig. 7 illustrates the results on 6 consecutive patients undergoing major surgery. It is apparent that whereas the preoperative fraction exhibited none or very little sodium-retaining potency and in one instance even caused an increased (Case 1) sodium excretion, postoperative fractions caused marked sodium retention in the adrenalectomized rat. Values of log $\frac{K}{Na}$ were from 150 to over 300 per cent of the preoperative controls indicating amounts of

sodium-retaining hormone equal in potency to 10-30 μg of desoxycorticosterone per 20-minute urine volume. Studies are currently in progress attempting to delineate the period during which aldosterone excretion is increased and its relationship to serum concentration and over-all sodium balance.

Other fractions recognized chromatographically: The use of chromatographic strips has enabled us to make some further observations of a preliminary nature concerning the steroid constituents of postoperative urine, and there is no doubt that further exploration of this technique will yield information of considerable value. In early experiments dealing with the chromatographic pattern of the urine of adrenalectomized, ovariectomized women, it was noticed that a specific band emerged when desoxycorticosterone was added to the replacement therapy.[50] This metabolite produced a bright red color when treated with antimony trichloride thereby distinguishing itself in rather spectacular fashion from other bands on the strip. It did not reduce silver nor react with any of the other color-producing reactions commonly applied to steroids. It was occasionally seen in the urine of normal individuals. Its

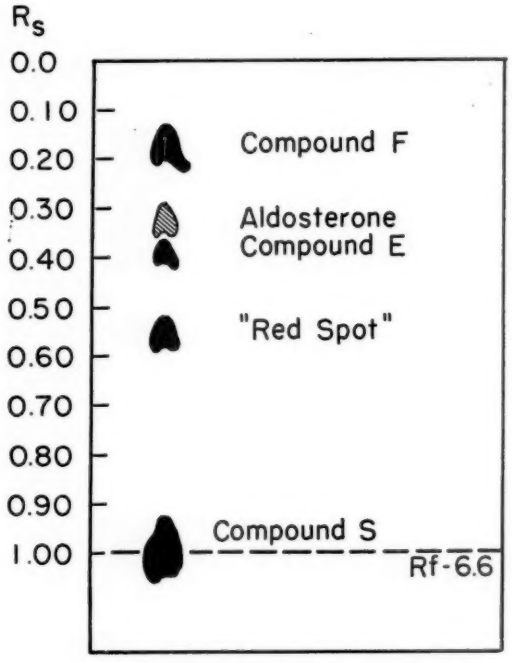

Fig. 8.—Diagramatic representation of chromatogram showing steroids mentioned in text.

$$Rf = \frac{\text{distance compound moves}}{\text{distance solvent front moves}}$$

$$Rs = \frac{Rf}{Rf \text{ of Reichstein's substance S}}$$

position relative to compound E, compound F, and aldosterone is indicated in the facsimile chromatogram shown in Fig. 8. Lacking the chemical identification of this substance, we have referred to it temporarily as the "red spot." Because of the consistent association of this spot with desoxycorticosterone administration in adrenalectomized individuals, it was of great interest to

observe what happened to it on the chromatograms of pre- and postoperative urine. Further studies must be done on this but in 11 cases so far studied, a measurable increase in intensity occurred in only three instances. A decrease in the "red" material occurred in 2 patients and in the remainder no change could be discerned. It appears, therefore, that it is not consistently related to surgical operations and this, in our minds, throws considerable doubt on the desoxycorticosterone theory despite the results of the pregnanediol experiments which indicated only that it could be present.

DISCUSSION

These experiments constitute only a beginning of the work which must be done before an exact chemical and physiological description of factors regulating sodium metabolism in the postoperative patient can be presented. Better methods will soon be available and the development of simpler and more exact techniques such as a chemical method for determination of aldosterone will tremendously facilitate advances in this field. Nevertheless, some interesting results have been obtained and already raise some rather intriguing theoretical problems. The finding of aldosterone in the postoperative urine satisfies some of the conditions that were predicted to be necessary for a sodium-retaining substance on the basis of the experiments recorded in the earlier part of this paper. Its regulation, according to the experiments of Luetscher, does appear to be independent of the anterior pituitary or at least it does not require ACTH for its mobilization. Although this fits well with the above-mentioned conditions, it raises a rather fascinating question. If ACTH stimulation does not cause an output of this material following trauma, what mediating mechanism is responsible? The implication of a second corticotrophic mechanism such as pituitary growth hormone is possible but seems unlikely in view of the fact that this material is present in normal amounts in hypophysectomized individuals.[54] At the moment it seems more probable that the mobilization of aldosterone is related directly to some quantity relative to the electrolytes in the plasma. This could be either the sodium level, potassium level, or perhaps the sodium-potassium ratio. If the serum sodium level is the critical factor, there may already be an explanation for its appearance in the postoperative patient. In the first section of the paper we discussed the rather consistent depression of the serum sodium which follows immediately after surgery. This effect occurs early during the first and second day and corresponds to the interval when high levels of urinary aldosterone were found.

In this connection it is of interest that Venning[50] reported no increase in aldosterone in some patients with fractures. The difference between our findings and hers may lie in the fact that in her experiments pretrauma controls were not available, or the time of measurement relative to the time of injury was somewhat later, or the routine type of postoperative fluid management was not being administered and some degree of dehydration may have prevented this sodium drop. Llaurado of Dunedin,[28] however, has recently reported findings similar to ours. In experiments now in progress an attempt is being made to test

the possibility that the serum sodium is the mediator of aldosterone output by investigating the relationship of the serum sodium as naturally or artificially manipulated to the urinary aldosterone level.

Finally, it should be mentioned that no single mechanism is likely to be responsible for the sodium retention which occurs following operations. Overlapping functions are characteristic of physiologic regulations and this is particularly true of endocrine substances which only accelerate or modify the course of processes for which the fundamental enzymatic machinery exists in cells. Ingle[23] has shown, for example, that adrenalectomized rats maintained on constant amounts of adrenal extract demonstrate changes in sodium and potassium balance when subjected to experimental fractures which are very similar to those observed in normal rats similarly traumatized. An increased amount of adrenal replacement at the time of stress is not necessary. We have carried out balance studies on two adrenalectomized patients who required elective surgery.[60] Adrenal replacement was maintained at a constant high level but not increased at the time of surgery. Although preoperative balance is difficult to establish under such circumstances, a relative retention of sodium and outpouring of potassium was discernible. It is apparent, therefore, that these processes can go on if adrenal replacement is adequate even in the absence of an acceleration of adrenal activity. This does not mean that the adrenal is unimportant but only that other mechanisms can compensate for the fluctuating characteristics of adrenal function during stress. The cardiac output is an example of such a mechanism which is profoundly altered during anesthesia and surgery. Its intimate relationship to renal sodium regulation is apparently independent of changing adrenal function.

SUMMARY

1. The internal distribution and the external balance of sodium ion is radically altered by major surgical operations. Despite rigorous limitation of urinary excretion of this ion, plasma levels tend to be low. Such depression is greater following large cancer operations than after standard procedures. Experimental evidence regarding the relative importance of water retention and internal translocation of sodium in the genesis of this picture has been cited.

2. Attempts have been made to isolate specific endocrine mechanisms responsible for the positive balance of sodium which characterizes the postoperative state. Evidence is presented which strongly suggests that such mechanisms can operate independently of the anterior pituitary.

3. Pregnanediol is excreted by male patients following surgery. This clearly indicates the mobilization of some steroid aside from the glycocorticoids exemplified by compound E (cortisone) and compound F (hydrocortisone). Though desoxycorticosterone is metabolized to pregnanediol, it is not the only possible precursor which could account for the appearance of this metabolite in the urine of postoperative patients. An antimony-reacting metabolite which is consistently related to desoxycorticosterone administration in adrenalectomized

individuals has not been present in the urine of a significant number of postoperative patients. This throws some doubt on desoxycorticosterone as a hormone related to sodium metabolism in surgical stress.

4. Material with the chemical, chromatographic, and pharmacologic properties of aldosterone has been found to be consistently increased in the urine of patients immediately following surgery. This substance satisfies the criteria of potent sodium retention and independence from the pituitary. Further studies of the chronologic pattern of aldosterone excretion and the mechanisms for its mobilization are currently under study.

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HEMOLYSIS AND TRANSURETHRAL RESECTION

A Review

C. D. Creevy, M.D., Minneapolis, Minn.

(From the Urological Division of the Department of Surgery, University of Minnesota Medical School)

TRANSURETHRAL resection of the prostate, properly done, is justly popular because it yields a more comfortable convalescence, a shorter stay in the hospital, and a lower mortality than do the various types of enucleation. Thus, the mortality in 2,760 enucleations collected from the literature between 1945 and 1950 was 5.3 per cent; that of 14,947 transurethral resections was but 1.29 per cent. Two associates and I, in 1950,[13] reported 1,000 consecutive cases with a death rate of 0.6 per cent.

Those who undertook to make resection as complete as enucleation occasionally saw postoperative renal failure not explicable by pyelonephritis, hemorrhage, shock, reactions to transfusion, nephrotoxic agents, or ureteral obstruction. In a casual conversation in 1946, Foley[22] said that he had seen red ureteral jets during transurethral prostatic resection, and had assumed that it was due to intravascular hemolysis from the distilled irrigating water. Emmett[19] then stated that McLaughlin had also theorized that irrigating fluid might enter the circulation.

A few days later a transurethral resection of 58 grams, performed by my associate Dr. E. A. Webb, was followed at once by cyanosis, stupor, oliguria, anemia out of proportion to the loss of blood, and jaundice (Table I). Within a few hours another associate, Dr. B. A. Smith, observed that the patient's plasma was dark red. The preoperative urea nitrogen had been slightly elevated. There was no severe hypotension at any time. Although peritoneal lavage controlled the postoperative uremia, the patient died from pulmonary edema due either to an unreasonably high intake of fluid in relation to the urine output or to its unobserved absorption through the peritoneum. At autopsy he had a hemoglobinuric nephrosis, although no transfusion had preceded the onset of the reaction. It seemed that the renal lesions resulted from the mechanism suggested by Foley and by Emmett, that is, hemoglobinemia from the distilled irrigating water.

The effects of severe hemoglobinemia upon the kidneys are well known. A sudden shrinkage of the kidneys in the experimental animal has been described by Mason and Mann,[37] by Hesse and Filatov,[30] and by Levy.[34] This is best explained by renal vasoconstriction mediated by the arrival of free hemoglobin in the renal vessels, and doubtless resulting in renal hypoxia. This in turn leads to pathologic changes consisting of pigmented casts in the convoluted and collecting tubules, the epithelium of which exhibits vacuolation, necrosis, and desquamation. While Lucké[35] claimed that only the distal segment of the nephron was involved, and so coined the euphonious term "lower nephron

nephrosis,'' Bell[3] has pointed out that the whole nephron distal to the glomerulus is affected. Similar changes have been seen after the experimental injection of solutions of hemoglobin by Levy, and of laked red cells by Barratt and Yorke.[2] Dunn and associates[16] have suggested that the ensuing oliguria and uremia result from the unselective absorption of glomerular filtrate by the injured tubules or by the surrounding interstitial tissue.

TABLE I. CLINICAL FEATURES OF HEMOGLOBINEMIA

1. Shock at onset?
2. Cyanosis at onset
3. Chills and low fever
4. Apathy
5. Anorexia, nausea and vomiting
6. Oliguria (edema later)
7. Azotemia
8. Nonobstructive jaundice
9. Late hypertension

Baker and Dodds[1] maintain that the tubules are plugged by casts of acid hematin (the exact composition of these casts has never been established), and that they can be prevented or dissolved by alkalinization of the urine. There is both clinical and experimental evidence that the reaction of the urine is not important. Foy and Kondi[24] saw anuria in blackwater fever with strongly alkaline urine; Flink[21] was unable to prevent renal injury in the dog from the injection of solutions of hemoglobin by preliminary alkalinization of the urine. Bell and others have pointed out that the number of pigmented casts is often insufficient to account for renal failure on the basis of obstruction alone, and have emphasized the importance of the tubular lesions.

Renal failure from hemoglobinemia has been described in blackwater fever by Barratt and Yorke[2]; in crush injuries by Bywaters and Beall[8]; in severe burns by Goodpastor and associates[25]; in obstetrical injuries by Paxson and associates[42]; in poisoning with drugs and chemicals by Fox and Ottenberg[23]; and in mismatched transfusions by many observers (Table II).

TABLE II. THE CAUSES OF LOWER NEPHRON NEPHROSIS

I. Exposure to noxious agents
A. Theapeutic
1. Transfusion of incompatible blood
2. Injection of distilled water (transurethral prostatic resection)
3. Administration of toxic drugs; sulfonamides, arsenicals; overdosage with alkalis (?)
B. Experimental
Injection of solutions of hemoglobin or laked blood
C. Accidental
Foods (mussels, toadstools)
Industrial chemicals
Isopropyl alcohol, carbon tetrachloride, potassium chlorate
II. Trauma
A. Crush injuries
B. Severe burns
C. Heatstroke
D. Paroxysmal (cold) hemoglobinuria
E. Obstetrical mishaps
III. Living agents
Malaria (blackwater fever)
IV. Unknown causes
Nontraumatic muscular ischemia

While we know that transurethral resection can cause hemoglobinemia, and that the latter can injure the kidneys, it is not clear why one patient will tolerate a fairly intense hemoglobinemia without apparent ill effects, while another will die in uremia in a comparable situation. There are many possible complicating factors to be considered. First of all, the mere entrance of a limited amount of distilled water into the circulation is not necessarily harmful, as has been pointed out by Krumbhaar,[32] Victor,[50] and others. It seems possible that it is a solution of hemoglobin which enters the circulation during transurethral resection (blood hemolysed by the distilled water in the bladder). Howere, O'Shaugnessy and associates,[40] Sellards and Minot,[47] and Schenk[46] have stated that fair quantities of free hemoglobin can be given intravenously to normal individuals, both human and animal, without much harm. Since patients have died from renal failure due to hemoglobinemias from a great variety of causes, one must look for factors which may aggravate the effect of free hemoglobin upon the kidneys.

Since the primary renal effect of hemoglobinemia appears to be the production of constriction of the intrarenal vessels, other conditions which have the same effect might logically be expected to intensify the unfavorable consequences of a hemolytic reaction. The hypotension of surgical shock and hemorrhage does so, as demonstrated by Phillips and associates[43]; Page and Corcoran[41] have shown that the rapid loss of blood can cause renal vasoconstriction even though the blood pressure is maintained at normal levels. Both of these factors may, of course, occur during transurethral resection. Maluf[36] has emphasized the importance of dehydration as well as shock in potentiating the effect of hemoglobinemia upon the kidneys. Anemia could be expected to intensify a reaction from vasoconstriction, and it is likely that pre-existing renal disease, particularly arterio- or arteriolosclerosis and cicatricial pyelonephritis, would do the same thing, because both impair the renal circulation. Goodwin and associates[26] have shown that hydronephrosis magnifies the severity of hemoglobinuric nephrosis in the dog. The effect of a large shower of virulent bacteria upon previously diseased kidneys, already the seat of vasoconstriction from some or all of the factors mentioned above, should not be underestimated. Feeney and I[14] have shown that transitory bacteremia is a common accompaniment of transurethral resection. Consideration of these possibilities makes it seem likely that hemoglobinemia can inflict grave injury upon the kidneys of one patient while leaving those of another relatively intact.

Once a severe hemolytic reaction has occurred, the problem is to keep the patient alive while the renal damage is repaired. Flink[21] and others have shown that regeneration of the damaged or destroyed epithelium begins at about the fifth day. While such measures as strict limitation of fluid, a protein-free diet with a high caloric intake to prevent protein catabolism, a low intake of potassium, and the judicious use of peritoneal lavage or of the artificial kidney may save patients with severe renal lesions, prevention of the reaction is much safer and more economical than treatment.

CLINICAL INVESTIGATION

The free hemoglobin of the plasma was measured before and after 106 consecutive transurethral resections using distilled water as the irrigating fluid. The maximum preoperative level was 28 mg. per cent, but postoperatively it rose as high as 490, with an average of 42 mg. per cent above the preoperative figure. To make sure that this rise did not result from some factor other than the nature and absorption of the irrigating fluid, the free hemoglobin of the plasma was measured before and after (1) neurosurgical operations with surgical diathermy, (2) a variety of abdominal operations, and (3) the intravenous administration of normal saline solution and of 5 per cent glucose. There were no significant changes.

Five (later four) per cent glucose then was used as the irrigating solution, both to ascertain whether this would prevent a rise of plasma hemoglobin, and to determine whether the irrigating fluid did enter the circulation. Ebert[17] had used it to prevent injury to the periprostatic and perivesical tissues in the event of extravasation during transurethral resection, so that it was known to be practicable. Measurement of the free hemoglobin of the plasma before and after 185 consecutive resections with this irrigating agent disclosed no evidence of hemolysis. The blood sugar was then measured before and after 63 such operations with distilled water for irrigation. It was unaltered. Similar determinations were then made in 76 cases with glucose for irrigation; there was an average rise of 117 mg. per cent, with a maximum level of 1,079. In this patient, making no allowance for oxidation or excretion during operation, a period of about an hour and one-half, it was apparent that at least a liter of fluid had entered the circulation. No diabetics are included in these series.

Dr. E. T. Bell then kindly reviewed sections of the kidneys of six patients dying after transurethral prostatic resection before the adoption of isotonic irrigating solutions. Pigmented casts and toxic degeneration of the tubules were found in two of the six pairs of kidneys.

Since the adoption of nonhemolytic irrigating solutions in 1946, my colleagues E. A. Webb, B. A. Smith, and, more recently, W. E. Price, and M. P. Reiser, and I have performed transurethral prostatic resection in 2,492 consecutive patients with 24 deaths, an over-all surgical mortality of 0.96 per cent. Women and children are not included. The syndrome of cyanosis, torpor, anemia, oliguria, jaundice, and uremia has not been seen during this time. Since our mortality before 1946 ranged from 3 to 4 per cent, the reduction has to be attributed to elimination of hemolytic reactions.

OBJECTIONS TO ISOTONIC FLUIDS

Berry and White[4] recognized no hemolytic reactions in two thousand resections, but their mortality rate was 3.5 per cent. Biorn and Greene[5] verified the occurrence of hemolysis, but doubted its importance. Others have made similar statements, for which there are three reasons: failure to recognize the consequences of hemolysis; drawing conclusions from too few cases; and use of a technique which does not expose the surgical capsule of the gland. This leaves a

thick layer of prostatic tissue, and so does not divide large veins, most of which are in the periprostatic plexus. While this may be done with good immediate results, long-lasting relief cannot be expected, since only a little regrowth will cause recurrence of obstruction. My own aim, not always achieved, is to duplicate a good enucleation in completeness in the interests of durable relief. This leaves a thin rim of prostatic tissue, and exposes patches of periprostatic fat as well as the open veins of the periprostatic plexus. Hemostasis is more difficult than with incomplete operations, but the low mortality and good functional results justify the method. Since extravasations of irrigating fluid large enough to elevate the whole floor of the bladder cause no trouble, it seems that Ebert was right in using isotonic fluid to prevent local injury by distilled water.

A second objection is offered by Robbins and associates[45] who claim that the use of isotonic irrigating fluid so clouds vision as to make satisfactory resection difficult or impossible. Since I have resected as much as 199 grams at one session, this view is clearly wrong. Actually, one has only to learn to place the objective of the telescope a little closer than formerly to the cut surface of the gland in order to compensate fully for the inevitable cloudiness of the medium. Residents who are required to use nonhemolytic solutions from the first do not complain of such difficulty, which is thus pretty obviously psychological.

Others state that isotonic solutions for irrigation are unnecessary because one can use such low pressure that nothing will enter the open veins. Since, according to Starling,[49] venous pressures average about 1 mm. Hg (a little more than 1 cm. of water), this is clearly absurd. An irrigating pressure of this order would permit no vision whatever.

A third group has suggested that isotonic fluid be used only *after* large veins have been opened. Aside from the nuisance and wasted time of switching irrigators during operation, there is the obvious fact that open veins may be overlooked for a long time both because the irrigating fluid flows into them so that no bleeding is visible, and because overhanging tissue may conceal them until the prostatic fossa has been smoothed off at the end of operation.

Ebert recommended a solution of urea for irrigation arguing that, since it was a normal constituent of blood and urine, it would not injure the red blood cells nor the cut surface of the prostate. He overlooked two facts: the surface epithelium of the prostate, which customarily protects the underlying tissues, is removed during operation, and the urea normally present in the blood is mixed with other agents which render the plasma isotonic to the red blood cells. Solutions of urea in distilled water added to the blood in vitro are just as hemolytic as water alone. The occurrence of hemolysis during resection with solutions of urea as irrigating agents has been reported by Credle, Warren, and Vest,[9] and by me.

ADVANTAGES OF ISOTONIC SOLUTIONS

The value of nonhemolytic irrigating fluids has been rather widely accepted. Some have complained that solutions of glucose are sticky, and that they coat the lenses of the telescopes so as to impair vision. Nesbit and Glickman[38] use

1.1 per cent glycine, a naturally occurring amino acid. Goodwin and associates[26] have recommended 3 per cent mannitol, and a solution containing a polyhydric alcohol, called Cytal,* has been marked.[29] All do the job, but a concentrate of 50 to 100 per cent glucose added to the irrigating water as needed to make a 4 per cent solution, has the advantages of cheapness and ready availability. While the resulting solution *is* sticky, it washes off readily. I have had no difficulty with coating of the lenses, probably because they are washed with soapy water at the end of each operation.

While I have observed transitory bacteremia at the end of 43 of 94 consecutive transurethral resections, or 45.7 per cent, when no antibiotics were used, this is not in itself conclusive proof that bacteria are actually washed into the open veins, because chills, fever, and bacteremia following ordinary urethral instrumentation are too well known to require documentation. Feeney and I[14] have reviewed the literature of this subject. However, the report of Bulkley and associates,[6] that bacteremia followed but 1.56 per cent of 128 consecutive transurethral prostatic resections, suggests to me that open veins are important. He works in a clinic in which the larger glands are enucleated; I suspect that no serious attempt is made to duplicate the completeness of enucleation with the resectoscope. Consequently, fewer large veins are opened, and bacteria do not have such ready access to the circulation. Grey's report[27] of 54.5 per cent of positive blood cultures at the conclusion of operation is more in accord with my own experience.

Since 1947 at least twenty-five authors have verified the occurrence of hemolysis during transurethral prostatic resection, and most of them have accepted the value of isotonic irrigating solutions. While all are cited in the bibliography, only a few will be mentioned specifically. Jessop and Lane[31] substantiated my observation that the blood sugar rises after resection when the irrigating fluid contains glucose, and added that the level of the blood sugar at the end of operation was directly related to the pressure of the irrigating fluid.

Wear[51] found that distending the bladder with a solution of Diodrast for a short time immediately after operation led to visualization of the kidneys by excretion, since there was no evidence of urinary reflux. I have verified the occurrence of this phenomenon with Neo-iopax. The validity of these observations is weakened by Maluf's report[36] that Urokon was absorbed from the intact bladder in sufficient concentration to yield an excellent urogram in a patient with bilateral cutaneous ureterostomies. Whether this results from some specific property of Urokon, or whether the two preceding cases resulted from absorption by the vesical mucosa, or represent delayed reflux, is not known.

Sjostrand[48] has found the alveolar carbon monoxide elevated in various hemolytic states, including those after transurethral resection; the exact significance of this observation is not clear.

Renner[44] saw acute pancreatic necrosis following transurethral resection, and attributed it to "proteolytic enzymes" from the prostate gland. Since proof of the relationship is lacking, coincidence must be considered.

*Cutter Laboratories.

Ferguson[20] has suggested that the heat generated by the high frequency current is a factor in producing hemolysis. This seems unlikely in view of my own observation that the free hemoglobin of the plasma did not rise after operations with isotonic irrigating solutions, nor in neurosurgical operations in which surgical diathermy was used.

More recent papers has discussed the absorption of fluid and its effect upon cardiovascular dynamics and the balance of fluids and electrolytes. Bulkley and associates[7] and Hagstrom[28] have reported sudden heart failure in patients with preexisting cardiac lesions, and unexpectedly high urine outputs in others following transurethral resection. They have attributed these occurrences to the absorption of large volumes of fluid through the prostatic veins. Landsteiner and Finch[33] estimated that one of their patients received at least 1,500 c.c. by this route. Our own attempts to estimate fluid absorption, except by calculations from the rise of blood sugar, failed for lack of a scale accurate enough to measure the small volumes involved in the average patient.

Murphy, Iob, and Lapides[37] studied fluid and electrolyte balance before and after operation in 11 patients, and concluded there is no alteration. Since we have encountered an example of acute hypochloremia with shock after resection in a presumably good risk, I suspect that their studies should be continued in a larger series of patients. One could do a hundred operations before encountering a really large inflow of fluid.

SUMMARY AND CONCLUSIONS

It has been known since 1946 that distilled water used to irrigate the bladder during transurethral prostatic resection hemolyses blood in the bladder and may propel it into the systemic circulation through open prostatic and periprostatic veins.

In the presence of pre-existing renal disease, of hypotension, or of rapid loss of blood, this may result in a hemolytic reaction indistinguishable from that due to the transfusion of incompatible blood.

Upon occasion enough fluid may enter the circulation to precipitate cardiac decompensation if cardiac dysfunction is already present; dilution of the blood by the same means may upset fluid and electrolyte balance, although this has not been proved.

The use of isotonic (nonhemolytic) irrigating solutions has materially reduced surgical mortality, as evidenced by the fact that my four colleagues and myself have, since the advent of these solutions, performed transurethral prostatic resection in 2,492 consecutive patients with 24 deaths, or 0.96 per cent.

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THE INTRADIAPHRAGMATIC DISTRIBUTION OF THE PHRENIC NERVE WITH PARTICULAR REFERENCE TO THE PLACEMENT OF DIAPHRAGMATIC INCISIONS AND CONTROLLED SEGMENTAL PARALYSIS

K. Alvin Merendino, M.D., Robert J. Johnson, M.D., H. H. Skinner, M.D., and R. X. Maguire, M.D., Seattle, Wash.

(From the Departments of Surgery and Anatomy, University of Washington, School of Medicine)

THE cervical origin and anatomic relationship of the phrenic nerves are well known. Anatomists and surgeons have interested themselves in this because cervical phrenicotomy, phrenicopraxia, and so forth, were commonly used in the treatment of tuberculosis. Consequently, considerable information is available concerning the proximal portion of the nerves. By contrast, there is meager or inaccurate knowledge of the intradiaphragmatic distribution of the phrenic nerve. This may be surprising to some, for there is a tendency to believe that all things of gross anatomical interest have been fully described. The vagueness of major works on anatomy is characterized by the latest edition of Gray's textbook[1] which states simply that "the terminal branches of the phrenic nerve pass through the diaphragm separately, and diverging from each other, are distributed on the under surface, supplying the diaphragmatic muscle and sensory fibers to the peritoneum." Grant's *Method of Anatomy*[2] gives no description of the course of the phrenic branches in the diaphragm, but a diagram is shown which clearly portrays the branches radiating peripherally from the point of diaphragmatic entry. There is a general belief that the branches of the phrenic nerve after it enters the diaphragm radiate like the spokes of a wheel. There is little to be gained by quoting other anatomic sources. Suffice it to say that some are at variance with others and, in certain respects, appear to be inaccurate in the light of the present study.

By the use of combined abdominothoracic incisions which of necessity have a diaphragmatic component, as well as the transthoracic transdiaphragmatic approach to abdominal viscera, there can be little doubt that the diaphragm unwittingly is totally or partially denervated. The loss of pulmonary function due to unilateral diaphragmatic paralysis is not a minor item. Particularly it may be of critical importance immediately postoperative in the borderline-risk patient. Here again the surgical need dictates an anatomical clarification of the distribution of the phrenic nerve in the diaphragm.

The present study was undertaken to determine the anatomic and physiologic distribution of the phrenic nerves, both in dogs and in human beings, in order to assist the surgeon in the placement of diaphragmatic incisions so as to avoid the needless sacrifice of diaphragmatic function with its undesirable pulmonic and extrapulmonic effects.

EXPERIMENTAL DATA IN THE DOG

Methods of Study.—A total of 80 hemidiaphragms (40 right; 40 left) have been studied. All were subjected to the stimulation of the various branches of the phrenic nerve as it terminates in the diaphragm. In addition, following stimulation, in 20 isolated hemi-

diaphragms (10 right; 10 left) the anatomic distribution of the terminal branches of the phrenic nerve was determined by gross dissection in the fresh state.

In the stimulation experiments essentially two methods were utilized:

Isolated specimens: Ten dogs were sacrificed and the entire diaphragm was removed immediately and completely by severance of its peripheral attachments. Each diaphragm then was pinned about its margin to a large pan of melted paraffin. Thus distortion was avoided. Also it enabled one to observe better the gross contractions following stimulation. The main branches of the phrenic nerve then were dissected immediately and electrically stimulated. Satisfactory responses were obtainable usually for periods of 20 minutes.

In situ specimens: An additional 30 dogs were anesthetized with intravenous Nembutal, intubated with an intratracheal tube, and placed on a positive pressure respirator. The thoraces were entered via a transsternal incision in the sixth intercostal space bilaterally. The phrenic nerves were freed of the pericardial sac and the latter's diaphragmatic attachments were severed. The primary branches of the phrenic nerve were isolated and divided. The distal ends were electrically stimulated.

In both types of experiments the branches were stimulated by a two per second stimulus of 1 volt intensity. The anatomic distribution of the nerve and the area of response were recorded on mimeographed charts of the diaphragm, made for this purpose.

RESULTS

Anatomic Findings.—(Fig. 1.) The terminology used for the dog is patterned after that suggested by one of us (R. J. J.)[3] from his studies of the human diaphragm.

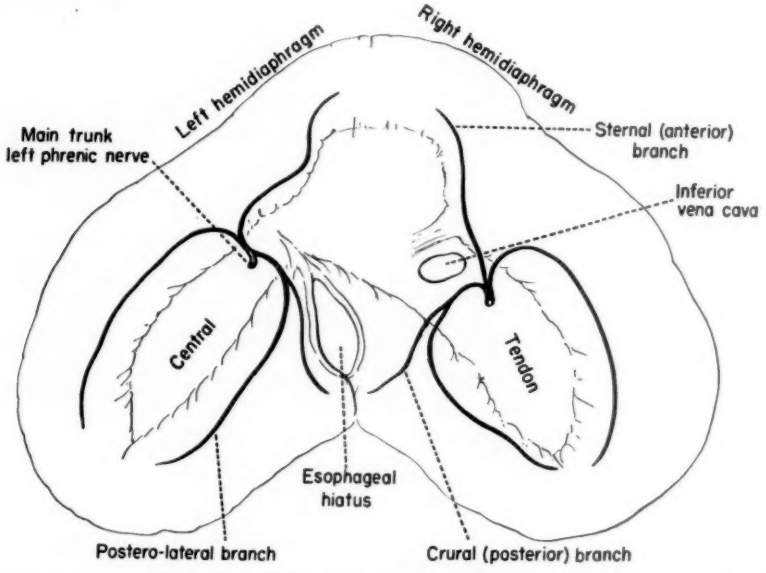

Fig. 1.—Dog. Viewed from above. The division of the phrenic nerves at the level of the diaphragm and the pattern of distribution of the major branches. This drawing emphasizes the double "handcuff" arrangement of the major branches. The anterolateral and posteromedial branches skirt the central tendon and encircle the dome.

The phrenic nerve divides into at least two component parts within 1 cm. of the superior border of the diaphragm: one trunk anterior which divides almost immediately into two parts; a sternal (anterior) and an anterolateral branch, and one trunk posterior, which generally turns and runs immediately beneath the parietal pleura toward the posterolateral portion of the diaphragm, usually dividing just before reaching the muscle substance into two branches; a crural (posterior) and a posterolateral. The crural branch on the left is not always constant, as it often appears as a small filament from the

main posterolateral branch. Within the muscle substance of the diaphragm the main nerve trunks lie much closer to the central, tendinous portion than to the periphery and the filaments passing to the various muscle groups or bundles *all* radiate costally, none extending toward the central tendon. The main nerve trunks do not appear to lie closer to the peritoneal than the pleural surface. Rather, they lie within a "stratum" approximately midway between the two surfaces. While frequently leaving at right angles to the main nerve trunks, the peripheral filaments usually are given off in such fashion so as to angulate laterad across several muscle fasciculi. The main trunks could not be traced satisfactorily to the extreme lateral margins of the diaphragm. Furthermore, no anastomotic connections of the antero- and posterolateral branches could be demonstrated.

The right phrenic nerve divides in much the same fashion as the left into two component parts, usually within 1 cm. of the superior border of the diaphragm. The anterior branch divides into sternal and anterolateral components as on the left. The posterior branch runs beneath the pleura as on the left, but generally separates quickly into definite crural and posterolateral components, with greater constancy than on the left. The crural branch is almost always present as a separate and definitive nerve trunk. The distribution of the nerve trunks relative to the muscular portion of the diaphragm is the same on the right as on the left.

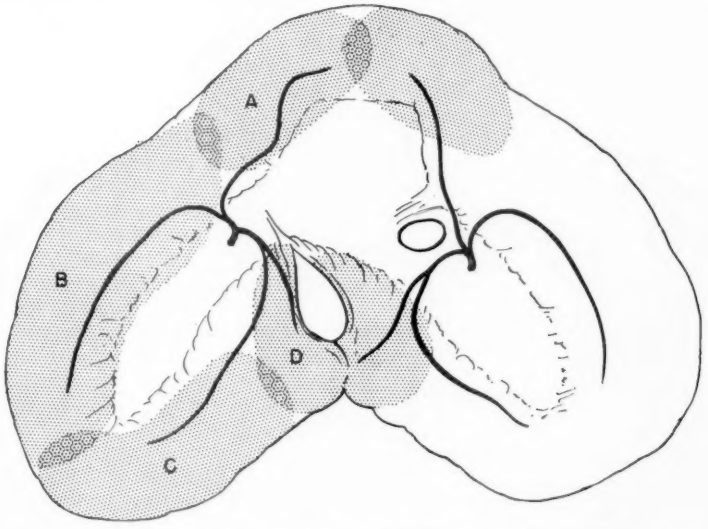

Fig. 2.—Dog. Viewed from above. Sphere of influence of each major branch upon electrical stimulation. The stippled areas indicate the segments of the diaphragm which contract upon stimulation of *A*, sternal (anterior) branch, *B*, anteromedial, *C*, posteromedial, *D*, crural (posterior). It will be noted that there is a small overlap in contraction with each branch. Anteriorly this extends into the opposite hemidiaphragm supplied by the right sternal branch. Apparently, there is very little overlap posteriorly in the crural branches.

Conduction Findings in the Dog.—(Fig. 2.) The stimulation of either main phrenic nerve trunk caused gross contraction of the ipsilateral hemidiaphragm with relatively little apparent overlap onto the contralateral side. What overlap there was appeared to be limited to the sternal (anterior) segments where some contraction of muscle fasciculi 1 to 2 cm. past the midline could be detected. There seemed to be almost no overlap of the crural (posterior) segments.

Sternal and anterolateral branches: Stimulated as one, before or proximal to the point of division into the two components, they exhibited the same degree of anterior midline overlap noted above as well as overlapping laterally into the posterolateral segment for a distance of about 2 cm. The sternal branch has the same overlap across the midline anteriorly, with about 1 cm. overlap into the anterolateral portion. The anterolateral branch has close to 2 cm. overlap into the anterior portion and about 2 cm. overlap laterally into the posterolateral portion. Technical difficulties in stimulating the anterior and anterolateral branches separately were considerable as there appeared to be a sort of "scatter" effect. This may have been due to the difficulty of achieving complete electrical isolation of the nerve filaments at the time of stimulation or, perhaps, to the use of too strong an electrical current.

Crural and posterolateral branches: Stimulated as one, proximal to the point of division into the two components, a 1 to 2 cm. overlap into the anterolateral portion was seen, with no appreciable overlap into the opposite crural portion. Due to the difficulty of obtaining a separate crural branch on the left, results were not too satisfactory. On the right, there was less than 1 cm. overlap into the posterolateral portion. On each side there was practically no appreciable overlap across the crus posteriorly.

Therefore, it is to be noted in the dog that the partition of the phrenic nerve as it enters the diaphragm is rather constant. The phrenic nerve characteristically divides into four major branches: sternal, anterolateral, crural, and posterolateral. The anterolateral and posterolateral branches skirt the central tendon and tend to approximate each other only at the lateral (midaxillary) diaphragm. This arrangement has been likened to a handcuff. As the course of both right and left nerves is the same, the distribution to the entire diaphragm may be considered to be a double handcuff pattern. While variations do occur, this is a satisfactory schematic concept.

Also, the anterolateral and posterolateral branches are the largest ones, pursue the longest course, and innervate most of the diaphragm. However, as one might suspect from the definite arrangement of branches, each of the four individual branches of both hemidiaphragms innervates a specific area which contracts when the branch is electrically stimulated. Consequently, the physiologic influence of each branch is segmental in nature with apparently only a minor overlap into adjacent portions of the diaphragm.

DATA ON MAN

Data obtained by gross dissection of human specimens and in the operating room correlate well with the information concerning the dog.

Gross Anatomy.—An anatomic study of the intradiaphragmatic distribution of the phrenic nerve by means of careful gross dissection was undertaken by one of us (R. J. J.). The results herein reported represent a preliminary summary based on some 40 human diaphragms. A more detailed analysis of these findings with further discussion of the many minor variations in the pattern of innervation will be presented elsewhere.

The right phrenic nerve reaches the diaphragm just lateral to the inferior vena caval aperture and at times may use that aperture as a route through the

diaphragm. The left phrenic nerve reaches the diaphragm just lateral to the left border of the heart and in a somewhat more anterior coronal plane than is the case for the right nerve. Instead of piercing the central tendon as does the right, however, the left nerve passes through the muscular portion of the diaphragm anterior to the central tendon.

Typically, the phrenic nerve (either the right or the left) divides at the level of the diaphragm, or a centimeter or two above it, into several terminal branches. Of these branches two or three are commonly very fine and are distributed to the serosal surfaces of the diaphragm, the pleura above, and the peritoneum below. These pleural and peritoneal twigs, when present as discrete branches, supply only the central serosal areas.

The greater mass of the dividing phrenic nerve continues entirely, or part of the way, through the diaphragm for its subsequent distribution as muscular rami. A few scattered filaments are given off from these muscular rami to the subjacent peritoneum. The muscular rami, here in the area where they pierce the diaphragm, vary from two to four in number. Fundamentally, there are four main rami and four major areas of distribution. A reduction in number is brought about by two branches sharing a common trunk for a short distance.

In the most common pattern three muscular branches arise directly from the phrenic nerve. One is directed anteromedially toward the sternum. Another is directed laterally anterior to the lateral leaf of the central tendon. The third branch is directed posteriorly and shortly divided into a branch which runs laterally posterior to the lateral leaf of the central tendon and into a branch which runs posteriorly and somewhat medially to gain the region of the crus. Thus a pattern of four major branches is seen with the two more posterior branches often having a short common trunk. These four branches may be named, respectively, the sternal or anterior branch, the anterolateral branch, the posterolateral branch, and the crural or posterior branch. Fig. 3 portrays a specimen which fairly closely follows this typical or "standard" plan. In the preparation of this figure the strongly curved surface of the diaphragm was projected onto a plane surface by extending the muscular portion out radially from the central tendon. The entire diaphragm was drawn life size. Conversion of the curved diaphragm into a plane figure inevitably results in some magnification of the peripheral portion in so far as circumferential measurements are concerned. It will be noted, from both Fig. 3 of an actual specimen and from Fig. 4, a schematization of the pattern in the human diaphragm, that the anterolateral and posterolateral branches of both the right and the left phrenic nerves form curves embracing the domes of their respective hemidiaphragms like the arms of a pair of manacles.

These muscular rami were often found to be submerged in the muscle substance rather than lying exposed on the inferior surface as commonly stated in textbooks. After the peritoneum and endoabdominal fascia were removed, many specimens revealed only segments of these muscular branches as the rami wended their way through the muscular substance, here and there appearing briefly at the surface or being seen only as terminal twigs supplying the peritoneum. As a crude estimate it might be said that 50 per cent of

the course of the muscular rami is a submerged one requiring the division of muscle fasciculi to expose the nerve.

Operating Room.—In patients subjected to a thoracic incision the terminal portion of the phrenic nerve has been isolated. By the nature of most clinical conditions, a left thoracotomy incision is more frequently used than a right. Consequently, most information gained from the operating room has been of the left phrenic nerve. However, there is no indication from the previous work presented that such information is not equally valid for the right phrenic nerve.

Anterior and posterior divisions of the phrenic nerve are readily demonstrable at the diaphragmatic level. Usually, three or four branches are pres-

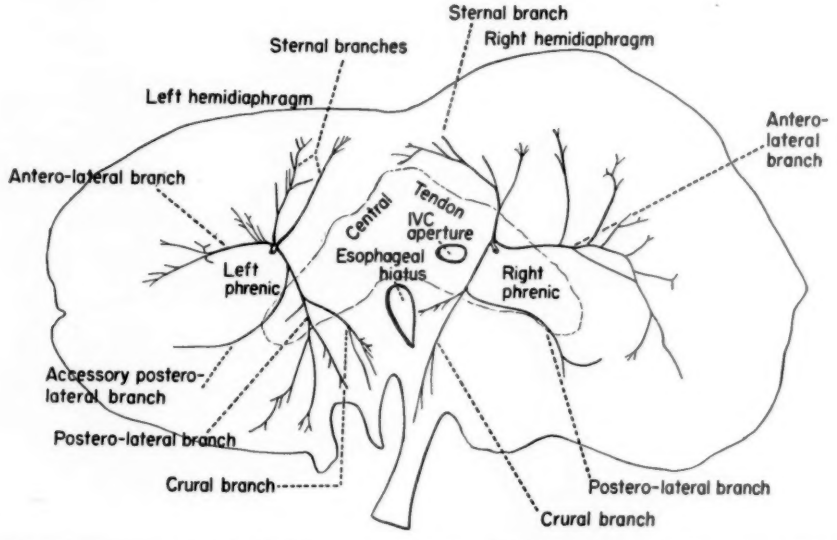

Fig. 3.—Human being. Actual findings in a gross dissection of a human diaphragm. This drawing is according to scale and viewed from above.

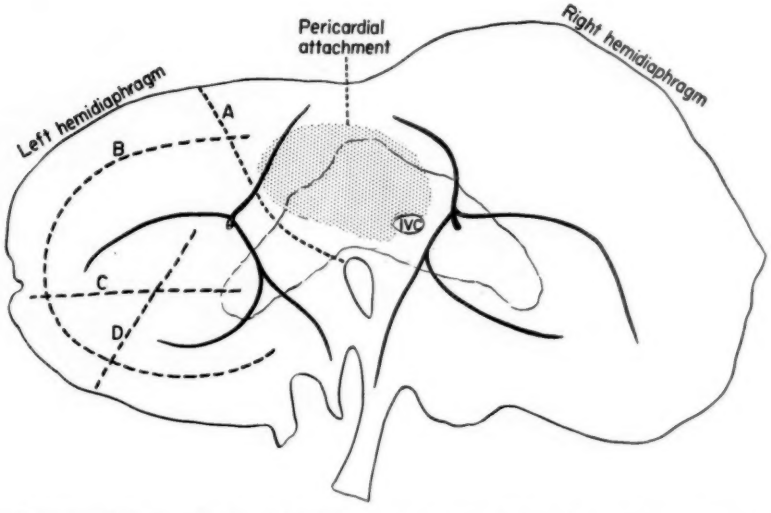

Fig. 4.—Human being. Schematized drawing indicating the "safe" areas in the diaphragm where incisions may be made without any significant effect on diaphragmatic function. *A*, indicates the diaphragmatic component of a combined abdomino-thoracic incision extending down into the esophageal hiatus. *B*, circumferential incision. *C* and *D*, incisions extending from lateral (midaxillary) and posterior costal areas into the central tendon (from above). See the text.

ent. By their size and anterior or posterior position, these are identifiable as sternal, anterolateral, posterolateral, and crural. The anterolateral and posterolateral divisions are always the larger trunks. If there is a single large branch anteriorly, by dissecting it a few centimeters, the sternal branch can be identified as it courses toward the sternum. Similarly, if the crural branch is not immediately apparent, by following this larger posterolateral branch, it will be observed to leave this main trunk and be directed toward the esophageal crus. On occasion, the crural branch was not identifiable. Undoubtedly, it takes off the posterolateral branch more distally than the dissection was carried out.

In patients subjected to pneumonectomy, these branches have been isolated and divided. Each has been repeatedly crushed in order to determine the area of contraction. In general, the area of contraction follows the identical pattern observed experimentally in dogs.

Practical Considerations.—Because of the rapid diminution in size of the branches of the phrenic nerve after they enter the diaphragm, it would be impractical to attempt to delineate the peripheral distribution of each individual nerve. Furthermore, as implied earlier, this is unnecessary. It is sufficient to know the four branches and the "handcuff" pattern created by the anterolateral and posteromedial divisions.

The placement of diaphragmatic incisions: This information indicates that there are "safe" areas in the diaphragm where incisions may be made with relative impunity and assurance that the branches of the phrenic nerve in the diaphragm will be preserved. If severance of a branch appears to be necessary, the denervation knowingly may be restricted to a small segment of the diaphragm.

Circumferential incisions anywhere in the periphery of the diaphragm result in little if any dysfunction of the diaphragm. Incisions through the central tendon, almost as far medially as the entrance of the phrenic nerve, can be made without the interruption of any major branch. Lateral or transverse incisions from midaxillary line medially likewise result in almost no paralysis. This incision is of use in transthoracic splenectomy.

Combined abdominothoracic incisions, if properly placed, do not significantly affect diaphragmatic function. When the abdominal and thoracic walls have been incised with severance of the costal cartilage, the diaphragmatic incision must extend medially and downward between the entrance of the phrenic nerve into the diaphragm and the pericardial attachment to the diaphragm. The diaphragm then can be opened down to and including the apex of the esophageal hiatus. In this fashion only the relatively unimportant sternal division will be severed. All other nerve components remain intact. When one begins to separate the ribs by forceful retraction, the attachment of the phrenic nerve, and the pericardiacophrenic vessels with their fatty components must be separated from the pericardium for 14 to 15 cm. proximally. Otherwise, the nerve filaments within the nerve sheath may be ruptured. When this precaution is observed, full exposure can be obtained with the phrenic nerve attached to the diaphragm which retains normal action. There is only the mild annoyance of working about the phrenic nerve, which is a small price to pay for its preservation (Fig. 4). The combined abdominothoracic approach extending through the diaphragm to the esophageal hiatus as commonly practiced is de-

picted in Fig. 5. This results in almost total diaphragmatic paralysis. Likewise, in combined incisions for splenorenal or portacaval anastomoses, full exposure can be obtained by incising the diaphragm circumferentially in its peripheral aspects. All the incisions described have been used routinely in the clinic for the past three years.

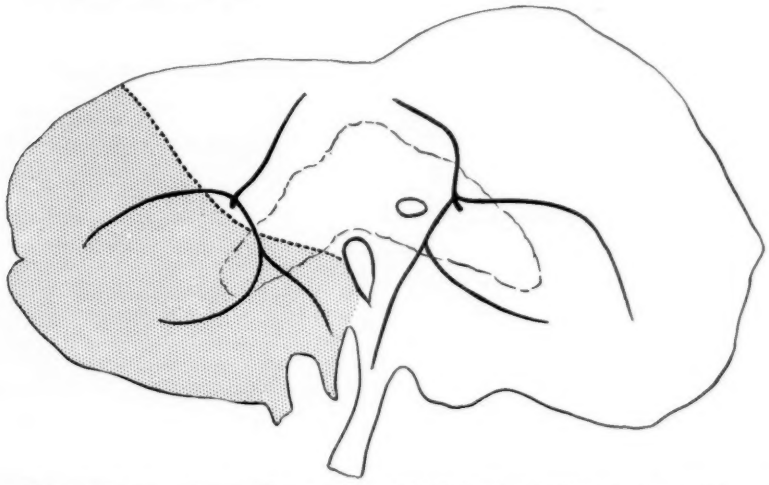

Fig. 5.—Human being. From above. The stippled area indicates the total and permanent loss in diaphragmatic function accompanying the usual diaphragmatic component of a combined abdomino-thoracic incision. This, obviously, should be avoided.

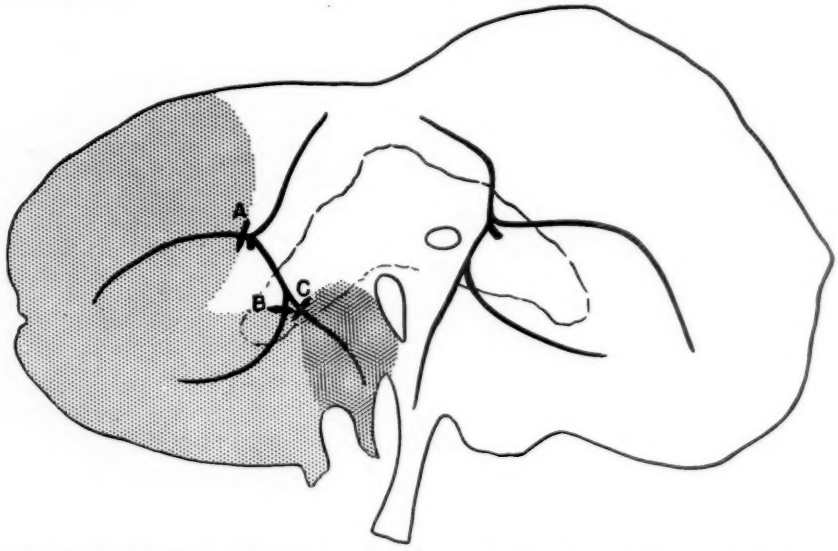

Fig. 6.—Human being. From above. This schematized drawing indicates the areas affected by controlled segmental paralysis. *A*, the anteromedial branch may be crushed to protect an anterior circumferential incision. *B*, posteromedial crush for a posterior circumferential incision. *C*, crural crush for hiatus hernioplasty (see the text).

Controlled segmental diaphragmatic paralysis: A common practice after diaphragmatic incision or reconstruction is to crush the entire phrenic nerve immediately above the diaphragm. The rationale for this maneuver is to rest the diaphragm "temporarily" in order to allow healing to occur and thus reduce the possibility of disruption of the suture line. From the studies herein presented it would appear that it is unnecessary in the ordinary case to ablate all diaphragmatic action in order to accomplish this. Diaphragmatic disruption fol-

lowing suture should be preventable by segmental paralysis of the area in which it is desired. For example, an anterior circumferential incision can be protected by crushing only the anterolateral branch. While it is true that the contraction of the remainder of the diaphragm still exerts a pulling force, it could hardly be considered disruptive, for the pull is exerted against a passive, segmentally paralyzed area. Similarly, it seems unnecessary following esophageal hiatus hernioplasty to crush the entire phrenic nerve at the diaphragm when one may crush the crural branch only. Here also, a pull may be exerted by the right crura; however, the net result is not disruptive for the left crura is capable of moving passively. The pull of the diaphragm by the posterolateral segment on the same side is not at right angles to the hiatus and, therefore, should affect this area in a minimal fashion only. If the crural branch is unidentifiable for any reason, the parent posterolateral branch may be crushed. However, this should be avoided if possible for the posterior portion of the diaphragm is of particular importance in pulmonary ventilation (Fig. 6).

DISCUSSION

Some, perhaps, may feel that too much stress has been placed upon the preservation of the phrenic nerve. However, the literature is replete with evidence of the importance of normal diaphragmatic action. It is frequently stated that in quiet breathing the diaphragm accounts for 60 per cent of the total air ventilated.[4] According to measurements of corpses, unilateral diaphragmatic paralysis decreased the volume of the hemithorax from 16 to 33 per cent.[5] Immediately following phrenic exeresis, an average decrease of 32.6 per cent in vital capacity in humans has been observed.[6] Others who evaluated the loss of pulmonary function subsequent to various thoracic procedures found that phrenic crush (14 days postoperative) was responsible for a 21 per cent loss of vital capacity and maximum breathing capacity, and an 18 per cent loss of O_2 uptake on the involved side.[7] In addition, there are extrapulmonic effects subsequent to phrenic interruption including the slowing of the venous return and gastrointestinal disturbance. The latter may be severe and permanent. Recently, one of us observed a case of severe esophagitis following left pneumonectomy with phrenic crush. The rise of the left diaphragm was followed by the stomach with apparently an adverse arrangement of the latter with the esophagogastric junction.

Furthermore, it is unrealistic to believe that phrenic crush is temporary, with a complete restoration of normal diaphragmatic function subsequently. In a study of 157 cases observed one year or longer after phrenic crushing operations, there existed some degree of permanent paralysis in approximately one-half of the cases and total loss of diaphragmatic function in one-fifth of the cases.[8] While pulmonary ventilatory loss may be compensated in part by the contralateral lung in time, the acute changes are the more critical ones in the immediate postoperative patient.

Today, constant stress is placed upon lowering the morbidity and mortality of surgical procedures. Considerable attention is paid to preventing the preventable death. The improvements in ancillary supporting fields tend to encourage boldness on the part of the surgeon. Extensive major surgical procedures are offered to a more aged patient population than heretofore. In

contrast to the surgery of some years back, death of the postsurgical patient is less frequently the result of a single gross error. It is an impression that more frequently today the patient dies not of a single complication, but often of the effects of multiple small complications which individually would not be lethal but when compounded result in a fatality. This presentation is an attempt to isolate one of these factors. There can be little doubt that the immediate loss of pulmonary function with its adverse effect on venous return and the gastrointestinal tract may be poorly tolerated by the borderline-risk patient. Few would deny the importance postoperatively of a good effective cough and the increased incidence of pulmonary atelectasis and bronchopneumonia secondary to an elevated atonic diaphragm. In the aged these factors may represent the difference between life and death.

It has been shown that phrenic interruption with diaphragmatic paralysis is a preventable complication. Furthermore, the concept of controlled segmental paralysis is a usable maneuver in the surgeon's hands.

CONCLUSIONS

1. The muscular fibers of the phrenic nerve, in both dog and man, are arranged in a fundamental pattern of four major rami: a sternal (anterior), an anterolateral, a posterolateral, and a crural (posterior).

2. By coalescence of the proximal portions of these major branches variations occur in the number of these branches at the diaphragmatic level.

3. The schematic pattern is best described as a double "handcuff" arrangement with the anterolateral and posterolateral branches being the main components skirting circumferentially and lateral to the dome.

4. By electrical stimulation the diaphragmatic contraction is noted to be segmental. The segment effected is dependent upon the anatomic area supplied by the stimulated branch. There appears to be a small overlap with each branch and anteriorly across to the opposite diaphragm. This may be artefact due to the strength of the impulse used.

5. By the proper placement of diaphragmatic incisions, the phrenic branches can be avoided and function of the diaphragm preserved. This should obviate certain postoperative complications attributable to phrenic paralysis.

6. Furthermore, if segmental paralysis of the diaphragm seems indicated, this can be accomplished by crushing individual branches rather than the entire phrenic nerve.

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